CONTENTS

# The American Journal of Medicine

VOL. IX AUGUST, 1950 NO. 2

## *Editorial*



## *Clinical Studies*



*Contents continued on page* 5

# *practical ideals in diabetes*

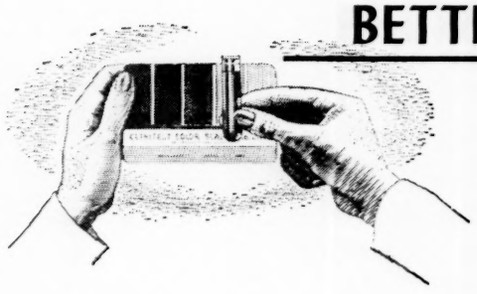
## EARLY DIAGNOSIS

"The ideal detection center is in the private physician's office."[1] This approach to widespread early diagnosis of diabetes can be practical when *every routine examination of every patient includes urine-sugar analysis.* Routine analysis, in turn, is more practical for the physician who uses *Clinitest* (Brand) Reagent Tablets. The test is simple, rapid and self-contained (no external heating). Results are known at once

# CLINITEST

**REAGENT TABLETS** ***for urine-sugar analysis***

## BETTER CONTROL



"Generally, only the well controlled diabetic patient may expect to live to normal expectancy and without premature arterial degeneration."[2] Here too, practicality recommends *Clinitest.* The *Clinitest* (Brand) Urine-sugar Analysis Set (a compact pocket unit) enables the patient, under the physician's guidance, to make regular checkups simply, accurately and conveniently. This is a practical guarantee of the patient's cooperation without which adequate control by the doctor is hardly feasible.

*Clinitest*, reg. trademark

**Bibliography:** (1) Wilkerson, H. L. C.: New York State J. Med. *49*:2945 (Dec. 15) 1949. (2) Sweeney, J. S.: Texas State J. Med. *45*:623 (Sept.) 1949.

**AMES COMPANY, INC. • ELKHART, INDIANA**
AMES COMPANY OF CANADA, LTD., TORONTO

CONTENTS

# The American Journal of Medicine

VOL. IX AUGUST, 1950 No. 2

*Contents continued from page 3*



## *Reviews*



## *Seminars on Renal Physiology*

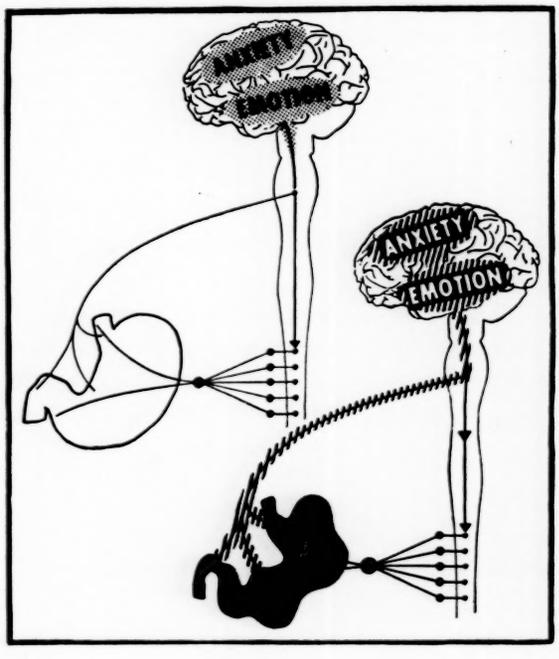


*Contents continued on page 7*

***". . . about 50% of the patients who consult the general practitioner have complaints for which there is no discoverable physical or organic cause."***[1]

**Emotional response and adaptation to stress** of the times play major roles in the increase of functional disorders. Exaggerated emotional response may produce somatic symptoms such as vague pains referred to various organs. Nausea, headache, cardiac and gastrointestinal distress are often presenting complaints. Diagnosis is usually easy in these cases because the number and variety of symptoms are not corroborated by physical findings. *Yet, these patients are seriously ill and merit attention and relief. Recent research has indicated that functional disturbances may develop into organic disease if long continued*[2]. In functional disorders, response to stress is effected via both branches of the autonomic nervous system. Therefore, treatment consists, where possible, in removal of the emotogenic factor (practical psychotherapy) and the "partial blockade" of the efferent autonomic pathways.

**The family physician is well qualified to help these patients** since he is most often aware of the environmental circumstances. His advice and guidance will do much to achieve the desired change in activities and habits and will help the patient to avoid "unhealthy situations".




**Medical treatment is also essential in most cases.** Controlled sedation of the entire autonomic nervous system accelerates recovery. This is accomplished by simultaneous administration of Bellafoline (cholinergic inhibitor), ergotamine tartrate (adrenergic inhibitor) and phenobarbital (central sedative).

Bellergal is a time tested preparation for administration in a wide variety of functional disorders. Bellergal inhibits the transmission of autonomic impulses without completely blocking organ function. This type of "mild sedation" will permit the patient to carry on daily activities while "taking stock of his difficulties". Karnosh and Zucker[3] state that, "Probably the best medication for all neurovegetative disorders is a combination of: (a) Bellafoline... (b) Ergotamine tartrate... (c) Phenobarbital... A good commercial preparation of these ingredients is a tablet called bellergal... The adult dose of bellergal is 3 or 4 tablets daily."

BIBLIOGRAPHY

1. WILLIAMS, V. P.: Medical Progress: Psychiatry, New England J. Med. *236:* 322-326 (Feb. 27) 1947.
2. NAIA, J. A.: Psyche and Somatic Disorders, Neurobiologia *9:* 269-278, 1946: Psychosom. Med. *10:* 120 (March-April) 1948.
3. KARNOSH, L. J. and ZUCKER, E. N.: A Handbook of Psychiatry, St. Louis, The C. V. Mosby Company, 1945, p. 248.

Brochures available on request:
"The A.N.S. and Functional Disorders."
"The Menopause Needs More Than Hormones."
"The A.N.S. and—Gastrointestinal Disorders—Cardiac Neuroses—Gynecological Problems—Anxiety States." (A series)

Sandoz Pharmaceuticals
DIVISION OF SANDOZ CHEMICAL WORKS, INC.
68 CHARLTON STREET, NEW YORK 14, NEW YORK

CONTENTS

# The American Journal of Medicine

VOL. IX AUGUST, 1950 NO. 2

*Contents continued from page 5*

## *Clinic on Psychosomatic Problems*



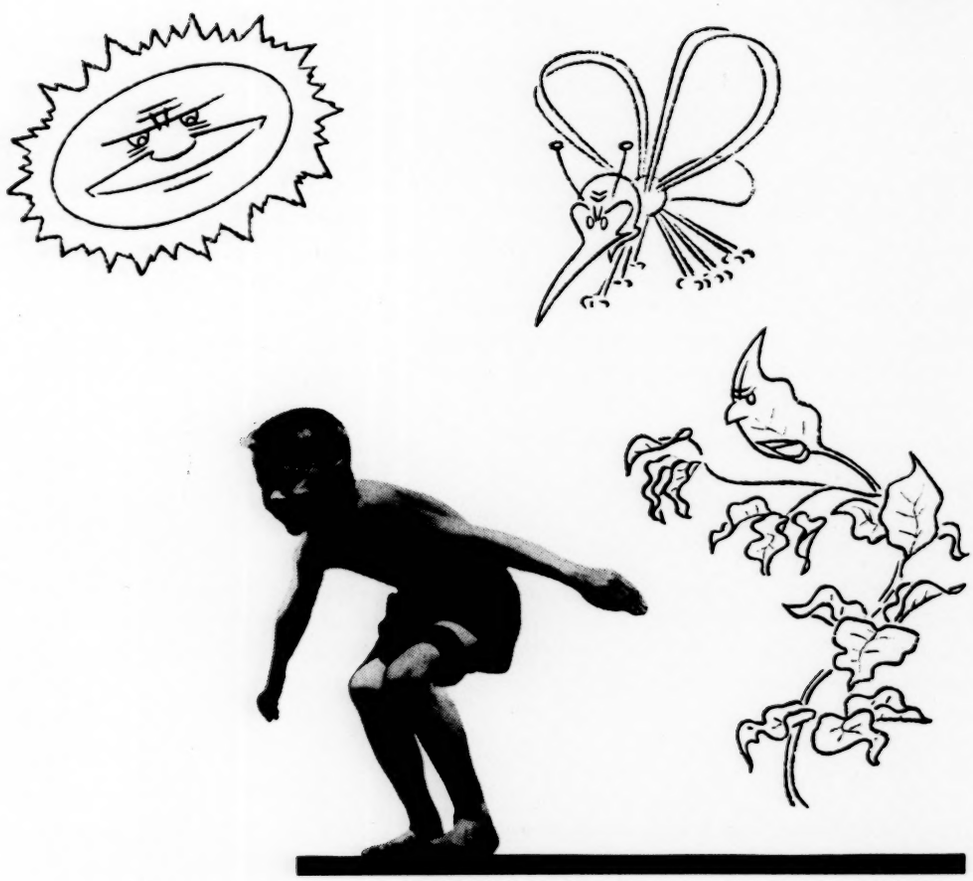
## *Clinico-pathologic Conference*



## *Special Feature*



## *Case Reports*



**Soothing antihistaminic in cream form**

## Cream
# NEOHETRAMINE®
Hydrochloride

For prompt relief
of itching due to:

- **SUNBURN**
- **INSECT BITES**
- **IVY POISONING**

**CONVENIENT TO USE:** rub gently into affected areas

**SUPPLIED:** CREAM NEOHETRAMINE HYDROCHLORIDE, 2%; in 1 oz. tubes

Neohetramine is the registered trademark of the Nepera Chemical Co., Inc., for its brand of thonzylamine—N, N-dimethyl-N' p-methoxybenzyl-N' (2-pyrimidyl) ethylenediamine.

*Wyeth* Incorporated • Philadelphia 3, Pa. Wyeth®

# AUREOMYCIN

CRYSTALLINE

## *in Infections of the Puerperium*

During the past year, obstetricians have become increasingly impressed with the ability of aureomycin to prevent or arrest infections of the puerperium. Where infection is feared, or has appeared, this broadly effective antibiotic is highly useful. Drug fastness and allergy are very rare following aureomycin. It is believed that this new crystalline form of aureomycin obviates nearly all side reactions.

Aureomycin

Aureomycin has also been found effective for the control of the following infections:

Acute amebiasis, bacterial infections associated with virus influenza, bacterial and virus-like infections of the eye, bacteroides septicemia, boutonneuse fever, brucellosis, chancroid, Friedländer infections (Klebsiella pneumonia), gonorrhea (resistant), Gram-negative infections (including those caused by some of the coli-aerogenes group), Gram-positive infections (including those caused by streptococci, staphylococci, and pneumococci), granuloma inguinale, *H. influenzae* infections, lymphogranuloma venereum, peritonitis, pertussis infections (acute and subacute), primary atypical pneumonia, psittacosis (parrot fever), Q fever, rickettsialpox, Rocky Mountain spotted fever, sinusitis, subacute bacterial endocarditis resistant to penicillin, surgical infections, tick-bite fever (African), tularemia, typhus and the common infections of the uterus and adnexa.

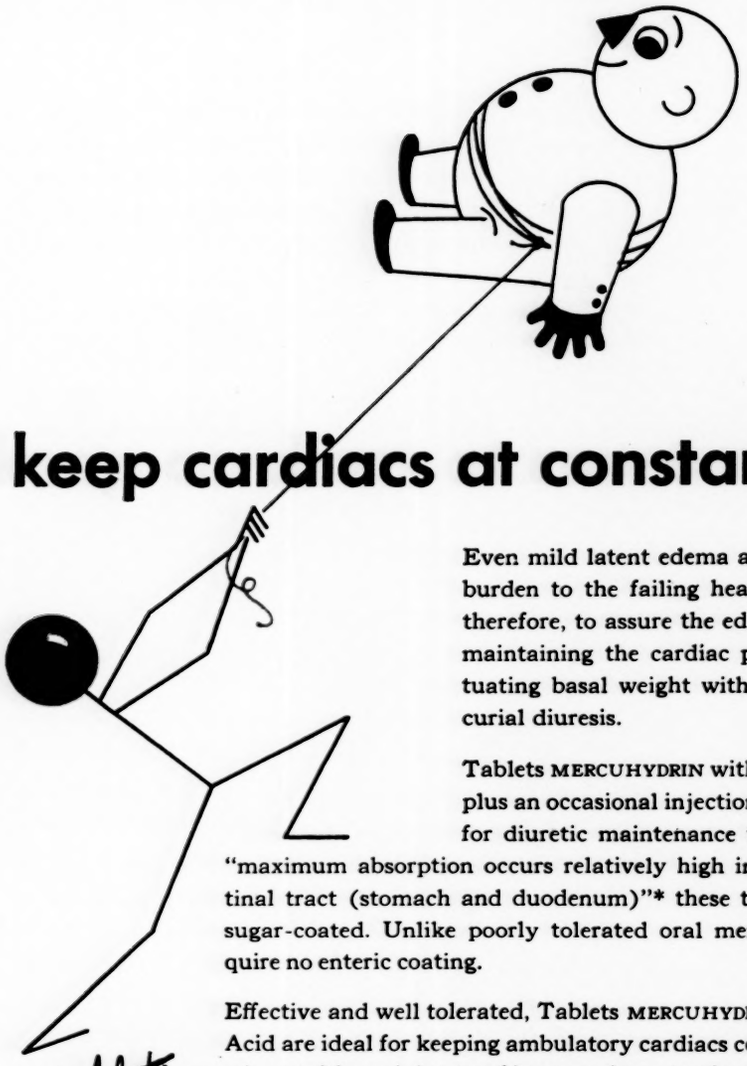
**Capsules:**
Bottles of 25, 50 mg. each capsule.
Bottles of 16, 250 mg. each capsule.

**Ophthalmic:**
Vials of 25 mg. with dropper, solution prepared by adding 5 cc. of distilled water.

LEDERLE LABORATORIES DIVISION

AMERICAN Cyanamid COMPANY

30 Rockefeller Plaza, New York 20, N. Y.



# keep cardiacs at constant weight

Even mild latent edema adds a substantial burden to the failing heart. It is the best, therefore, to assure the edema-free state by maintaining the cardiac patient at unfluctuating basal weight with systematic mercurial diuresis.

Tablets MERCUHYDRIN with Ascorbic Acid—plus an occasional injection—are unexcelled for diuretic maintenance therapy. Because "maximum absorption occurs relatively high in the gastrointestinal tract (stomach and duodenum)"* these tablets are simple sugar-coated. Unlike poorly tolerated oral mercurials, they require no enteric coating.

Effective and well tolerated, Tablets MERCUHYDRIN with Ascorbic Acid are ideal for keeping ambulatory cardiacs consistently free of edema with a minimum of inconvenience to physician and patient.

*tablets*

## MERCUHYDRIN®

**with Ascorbic Acid**

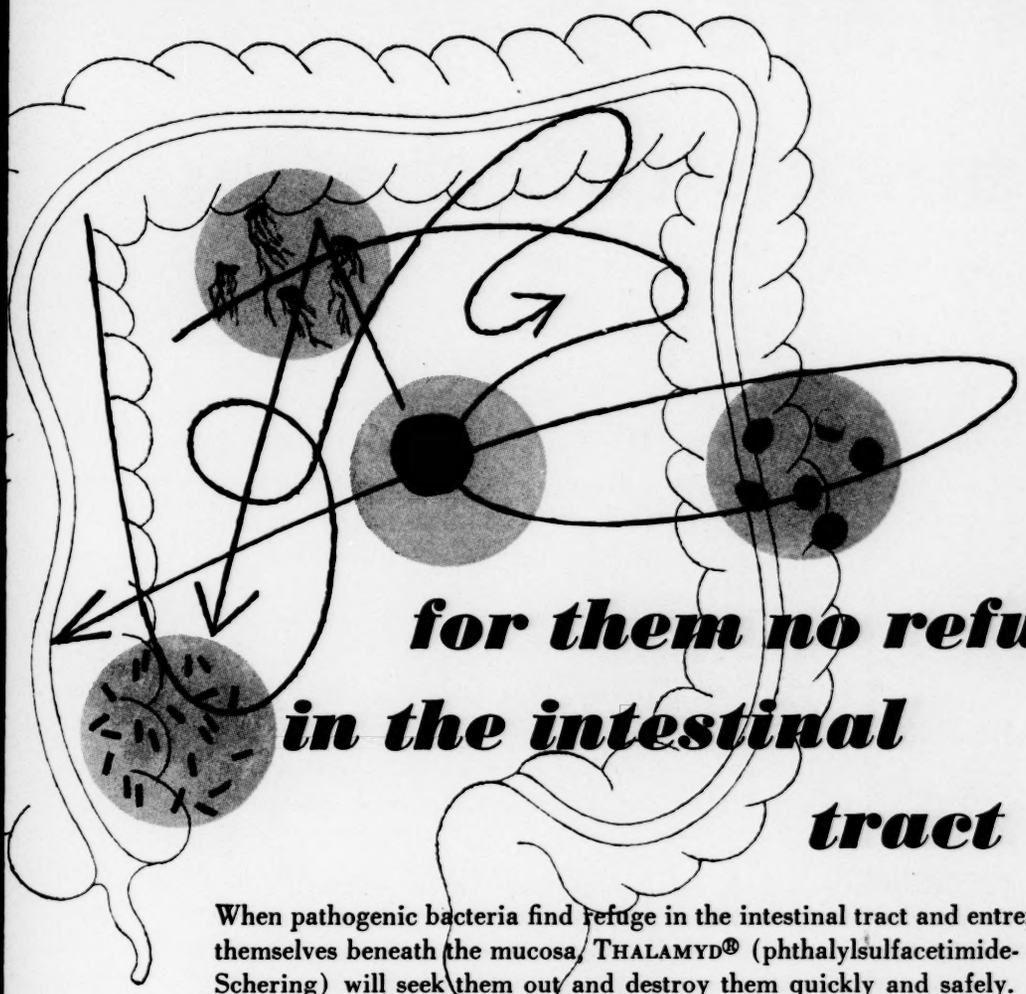
(brand of meralluride)

Available in bottles of 100 simple sugar-coated tablets each containing meralluride 60 mg. (equivalent to 19.5 mg. of mercury) and ascorbic acid 100 mg.

*Overman, W. J.; Gordon, W.,H., and Burch, G. E.: Tracer Studies of the Urinary Excretion of Radioactive Mercury following administration of a Mercurial Diuretic, Circulation *1*:496, 1950.

***The simplest method of outpatient maintenance***

*Lakeside Laboratories*, INC., MILWAUKEE 1, WISCONSIN



## *for them no refuge in the intestinal tract*

When pathogenic bacteria find refuge in the intestinal tract and entrench themselves beneath the mucosa, THALAMYD® (phthalylsulfacetimide-Schering) will seek them out and destroy them quickly and safely. THALAMYD is highly effective against most gastrointestinal pathogens whether they are within the lumen of the gut or have penetrated the muscularis. A nonabsorbable sulfonamide, THALAMYD is unique in being able to diffuse into the bowel wall, but not into the blood stream.

# THALAMYD

**(Phthalylsulfacetimide)**

More efficient than other nonabsorbable compounds, yet safer than absorbable drugs, THALAMYD is indicated in enteritis, dysentery due to Shigella and other susceptible organisms, ulcerative colitis and preoperative sterilization of the gastrointestinal tract.

**Packaging:** THALAMYD (phthalylsulfacetimide) Tablets 0.5 Gm. Bottles of 100 and 1000 tablets.

*Schering* CORPORATION · BLOOMFIELD, NEW JERSEY

THALAMYD

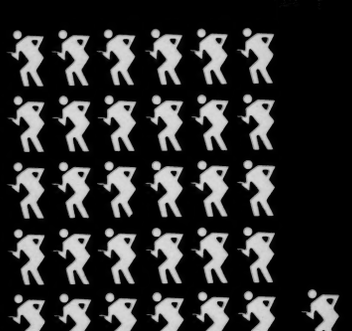
SCHERING

# PABALATE®

## CLINICAL EFFICACY

Percentage of rheumatic cases for which various dosages were required for effective relief

## PROLONGED (24 HOUR) RELIEF



SODIUM SALICYLATE 72% PABALATE 2.4%

Percentage of patients in whom need for next dose preceded scheduled administration

## COMPLETE FREEDOM FROM TOXICITY

SOD. SALICYLATE 55.2% PABALATE 0%

Percentage of patients exhibiting by effect

# *antirheumatic superiority . . .*

"The greater efficacy of this preparation is clearly manifested when one considers that whereas only sixty-eight per cent of the patients got relief from 0.6 Gm. doses of sodium salicylate, ninety-two per cent got equal relief on the same dosage of sodium salicylate in the form of Pabalate, probably because of its para-aminobenzoate component. Toxicity was not reported by any of the patients during the administration."

— *Journal-Lancet*
*70:192, 1950*

Experience in the administration of the antirheumatic Pabalate confirms the efficacy, reliability and safety[6] of its synergistic combination of salicylate and para-aminobenzoic acid.[1,2,3,4,5] Pabalate has been reported not only to provide "twenty-four hour pain relief,"[6] but its use (unlike that of salicylate alone) carries a high degree of freedom from toxic reactions.[6]

**INDICATIONS** rheumatoid arthritis, fibrositis, acute rheumatic fever, gout, osteoarthritis. The Liquid is also recommended as a replacement for analgesic-antipyretic medication generally.

**FORMULA** each Pabalate Tablet or each 5 cc. (one teaspoonful) of Pabalate Liquid contains sodium salicylate, U.S.P. (5 grs.) 0.3 Gm.; para-aminobenzoic acid (as the sodium salt) (5 grs.) 0.3 Gm.

**SUPPLIED** Pabalate Tablets are supplied in bottles of 100 and 500; Pabalate Liquid in pints and gallons.

**REFERENCES**


1. Beckman, H.: Treatment in General Practice, 6th ed., W. B. Saunders Co., Phila., 1948.
2. Belisle, M.: Union méd. du Canada, 77:392, 1948.
3. Dry, T. J. et al.: Proc. Staff Meet., Mayo Clin., 21:497, 1946.
4. Rosenblum, H. and Fraser, L. E.: Proc. Soc. Exper. Biol. & Med., 65:178, 1947.
5. Salassa, R. M., et al., J. Lab. & Clin. Med., 33:1393, 1948.
6. Smith, R. T.: J. Lancet, 70:192, 1950.


**A. H. ROBINS CO., INC., Richmond 20, Va.**

***Ethical Pharmaceuticals of Merit since 1878***

**PABALATE®** Robins

**The data for these graphs are derived from the tabular material accompanying *"Treatment of Rheumatoid Arthritis and other Rheumatic Conditions with Salicylate and Para-Aminobenzoic Acid: a study of 125 patients."* by Richard T. Smith, J. Lancet, 70:192, 1950.

# RUTAMINAL*

the protection of **rutin**[1] the action of **aminophylline** the sedation of **phenobarbital** —for use in selected cardiovascular and diabetic conditions in which excessive capillary fragility presents a complicating hazard —bottles of 100 tablets

Ocular Fundus in Degenerative Vascular Disease—Hypertension, Diabetes, Arteriosclerosis —note tortuous blood vessels, areas of exudation, hemorrhagic areas.

Normal Ocular Fundus

[1]In keeping with newer clinical findings, the rutin content of RUTAMINAL has been increased to 60 mg. per tablet (three times the former rutin content) at no increase in cost to the patient.

*RUTAMINAL is the trademark of Schenley Laboratories, Inc. and designates exclusively its brand of tablets containing rutin, aminophylline, and phenobarbital.

**schenley** laboratories, inc., 350 fifth ave., new york 1, n. y.

*Triple treatment for*

*DIARRHEA*

(specific and nonspecific)

# Cremosuxidine®

Suspension of

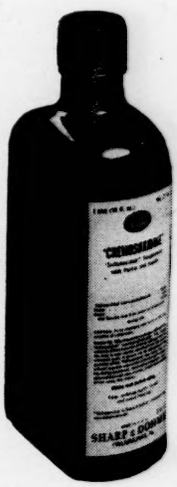
1 *Sulfasuxidine®* succinylsulfathiazole, 10.0%

2 *Pectin*, 1.0%

3 *Kaolin*, 10.0%

SHARP & DOHME

Diarrhea is a nuisance, "one of the commonest symptoms of illness in the human race,"* and a real menace, accounting for nearly 1% of deaths reported in the United States. In ten Southern states, in 1946, more deaths were reported due to diarrhea than to typhoid and scarlet fevers, pertussis, diphtheria, malaria, measles, and poliomyelitis combined!* *Cremosuxidine®* offers a new, palatably flavored, exceptionally effective triad for control of specific and nonspecific diarrheas: potently bacteriostatic, relatively nontoxic *Sulfasuxidine®*, detoxicant *pectin*, and protective, adsorbent *kaolin*. *Cremosuxidine* may be administered for bacillary dysentery, paradysentery, salmonellosis, diarrhea of the newborn, and so-called "summer complaint." Supplied in *Spasaver®* bottles containing 16 fluidounces. Sharp & Dohme, Philadelphia 1, Pa.



*Gray, A. L.: Southern Med. J., 43:320, April, 1950.

# If she reads a menu from the *bottom up*

SHE may not always be scrupulous about following the prenatal or postnatal diet—good reason to prescribe DICALDIMIN as a supplementary source of necessary minerals and vitamins.

Your patients will appreciate DICALDIMIN'S convenience—average dose is one or two moderate-sized capsules with each meal. You'll appreciate its sound, comprehensive formula. Three DICALDIMIN Capsules daily supply:

- Generous amounts of calcium and phosphorus
- Sufficient vitamin D to meet the entire daily requirement during pregnancy and lactation.
- Twice the amount of iron and nicotinamide recommended for pregnant women.
- More than 3 times the recommended amount of riboflavin.
- Six times the recommended amount of thiamine.

In addition to the above, DICALDIMIN WITH VITAMIN C provides 50 mg. ascorbic acid.

Just in case some patients may not adhere strictly to diet, why not prescribe one of these supplements? Both DICALDIMIN and DICALDIMIN WITH VITAMIN C are available in bottles of 100, 500 and 1000 capsules, at pharmacies everywhere. Abbott


see that the Rx reads:

**DICALDIMIN®**

**(ABBOTT'S Dicalcium Phosphate with Vitamin D, Iron and Vitamin B Complex Factors)**

*new*

# Terrabon

***Brand of TERRAMYCIN ELIXIR***

***provides:*** Terramycin: 250 mg. per teaspoonful (5cc.)

cherry-color appeal

mint flavor 

*unique*

TERRABON* presents the only broad-spectrum antibiotic available as an elixir and in such potency. Since 1 teaspoonful (5cc.) is equal in Terramycin content to one 250 mg. capsule, *therapy with the elixir does not require new and unwieldy dosage schedules.*

***the preferred dosage form for*** { Pediatric Patients; Geriatric Patients; "Sensitive" patients who experience difficulty in taking the customary forms of oral antibiotic medication.

The *palatability and pharmaceutical elegance* of TERRABON *add appeal* to the *broad antimicrobial activity, wide clinical effectiveness,* and *high toleration* of

***Terramycin—newest of the broad-spectrum antibiotics.***

***Terrabon Dosage:*** One teaspoonful (5cc.) of Terrabon is equal in Terramycin content to one 250 mg. capsule. In adults and older children, 2 to 3 Gm. daily in divided doses q. 4 or 6 h. is suggested. In children under 20 Kg. body weight, suggested dosage is 100 mg./Kg. body weight per day.

***Supplied:*** Terrabon is available as a combination package consisting of:

1. A vial containing 1.5 Gm. of Terramycin as Terramycin Hydrochloride.
2. A bottle containing 1 fluid ounce of specially buffered and flavored diluent.

***Also Available:*** Crystalline Terramycin Hydrochloride in 3 convenient capsule sizes:

250 mg., bottles of 16 and 100;
100 mg., bottles of 25;
50 mg., bottles of 25.

**Trade Mark*

**Pfizer**

***Antibiotic Division***
**CHAS. PFIZER & CO., INC.,** *Brooklyn 6, N. Y.*

# Molybdenized Iron... The Most Effective Iron Therapy Known...

*White's* Mol-iron®

## NOW ALSO with LIVER AND VITAMINS (*including B12*)

For iron-deficiency anemias associated with excessive drain on nutritional reserves—e.g., in chronic infection, malignancy, prolonged anorexia, post-surgical and other convalescent states—iron alone may not be sufficient.

**Mol-Iron with Liver and Vitamins provides, in each capsule:**

| | |
|---|---|
| Mol-Iron | 198 mg. |
| Desiccated Whole Liver (equivalent to 1.8 Gm. whole liver—minus water content only—not a fraction or an extract) | 0.45 Gm. |
| Thiamine hydrochloride | 1 mg. |
| Riboflavin | 1 mg. |
| Vitamin $B_{12}$ | 1 μg. |
| Nicotinamide | 5 mg. |
| Pyridoxine hydrochloride | 0.5 mg. |
| Calcium Pantothenate | 1 mg. |

Supplied in bottles of 100 capsules. Average dose 1 to 2 capsules three times daily after meals.

WHITE LABORATORIES, Inc., Pharmaceutical Manufacturers, Newark 7, N. J.

# SUPERIOR

PENICILLIN THERAPY WITH

# Penicillin S-R

TRADE MARK

**S** *oluble*

*plus* **R** *epository penicillin*

### *for the physician*

faster, higher initial levels... prolonged, high maintenance levels... better control of infection... quickly injected

### *for the nurse*

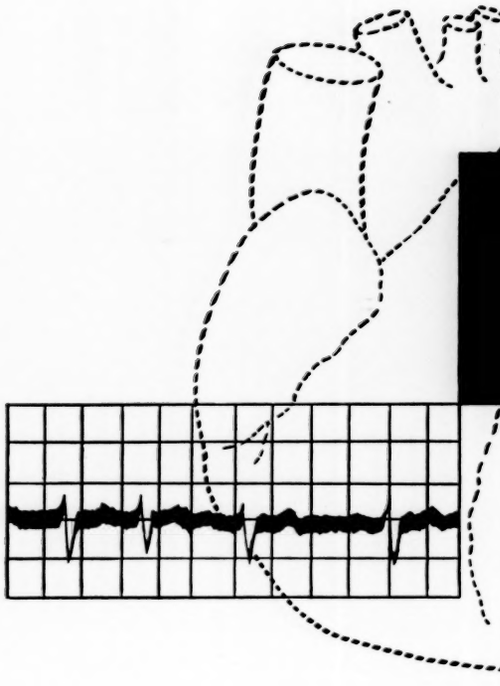
easily prepared... aqueous diluent... no vigorous shaking... free-flowing in syringe and needle

### *for the patient*

no sensitizing diluents... complete absorption – no wax or oil... minimal pain

Penicillin S-R is supplied in one-dose (400,000 units), five-dose (2,000,000 units) and ten-dose (4,000,000 units) vials. When diluted according to directions, each cc. contains 300,000 units of crystalline procaine penicillin-G and 100,000 units of buffered crystalline sodium penicillin-G. The one-dose vial is also available, if desired, with an accompanying ampoule of Water for Injection, U.S.P. Potency of the suspension is maintained for seven days at refrigerator temperatures.

PARKE, DAVIS & COMPANY



# DIGOXIN

'B.W.&Co.'

*A pure crystalline glycoside derived from Digitalis lanata*

Digoxin has been selected for use in fundamental studies on the hemodynamics of heart failure[1] and as a glycoside of choice for practical clinical treatment of heart failure[2] and auricular flutter.[3]

Harvey et al.[1] stated that in patients with left-sided heart failure "Digoxin produced a significant rise in cardiac output and stroke volume accompanied by a decrease in pulmonary arterial pressure."

Schaaf et al.[3] have concluded from their studies at the Massachusetts General Hospital that in the treatment of auricular flutter "digoxin was preferred to digitoxin or digitalis for this purpose because of its greater margin of safety."

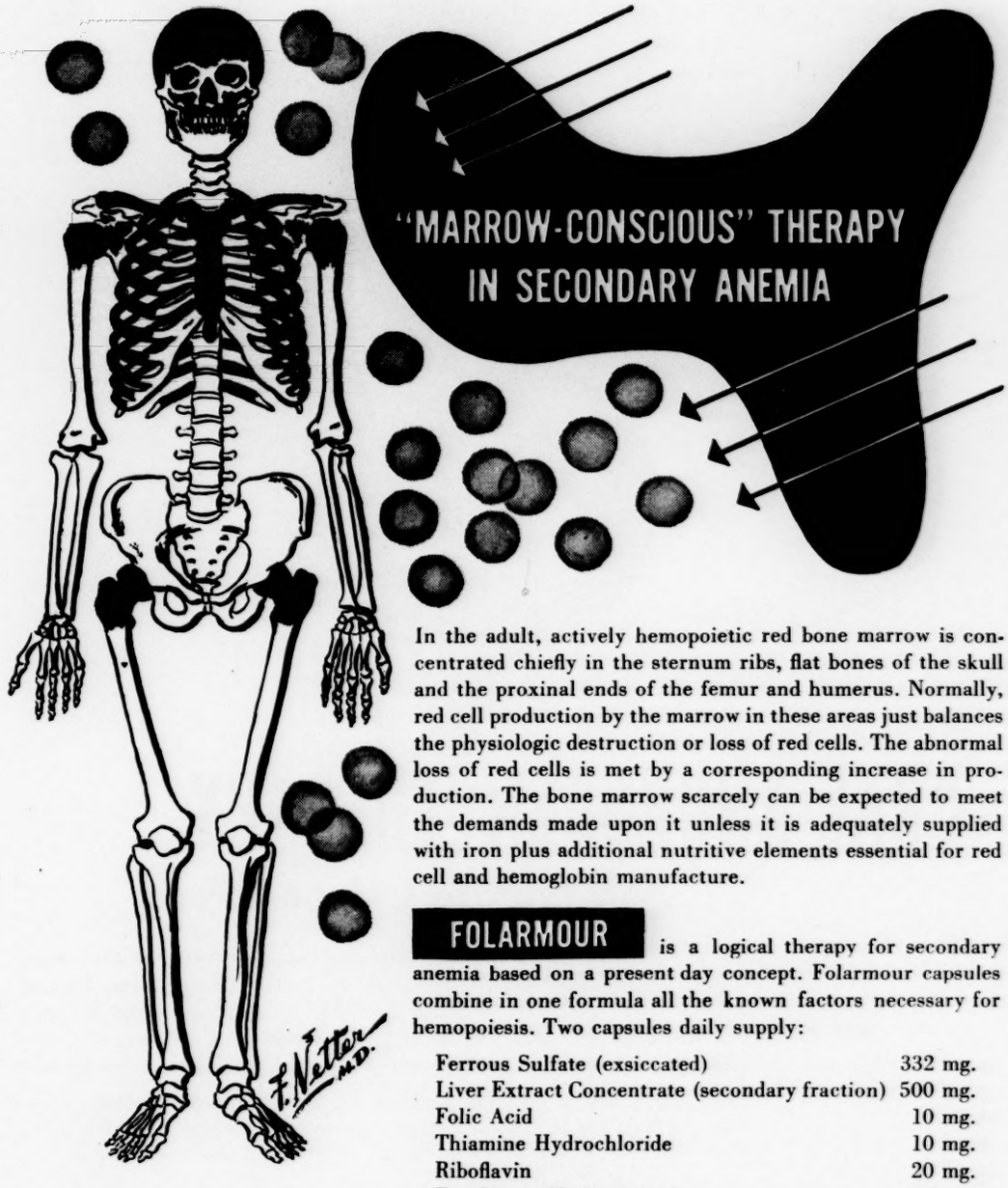

1. Harvey, R.M.; Ferrer, M.I.; Cathcart, R.T.; Richards, D.W., and Cournand, A.: Some Effects of Digoxin upon the Heart and Circulation in Man: Am. J. Med. 7:439 (Oct.) 1949.

2. Batterman, R.G., and DeGraff, A.C.: Comparative Study on the Use of the Purified Digitalis Glycosides, Digoxin, Digitoxin, and Lanatoside C, for the Management of Ambulatory Patients with Congestive Heart Failure: Am. Heart J. *34*:663 (Nov.)1947.

3. Schaaf, R.S.; Hurst, J.W., and Williams, C.: The Management of Auricular Flutter: Med. Clin. N. Am. p. 1255 (Sept.) 1949.


**BURROUGHS WELLCOME & CO.** (U.S.A.) INC.

TUCKAHOE 7, NEW YORK




Shaded areas indicate zones of active red bone marrow in the adult human.

In the adult, actively hemopoietic red bone marrow is concentrated chiefly in the sternum ribs, flat bones of the skull and the proxinal ends of the femur and humerus. Normally, red cell production by the marrow in these areas just balances the physiologic destruction or loss of red cells. The abnormal loss of red cells is met by a corresponding increase in production. The bone marrow scarcely can be expected to meet the demands made upon it unless it is adequately supplied with iron plus additional nutritive elements essential for red cell and hemoglobin manufacture.

**FOLARMOUR** is a logical therapy for secondary anemia based on a present day concept. Folarmour capsules combine in one formula all the known factors necessary for hemopoiesis. Two capsules daily supply:

| | |
|---|---|
| Ferrous Sulfate (exsiccated) | 332 mg. |
| Liver Extract Concentrate (secondary fraction) | 500 mg. |
| Folic Acid | 10 mg. |
| Thiamine Hydrochloride | 10 mg. |
| Riboflavin | 20 mg. |
| Pyridoxine Hydrochloride | 0.2 mg. |
| Niacinamide | 150 mg. |
| Calcium Pantothenate | 5 mg. |
| Ascorbic Acid | 150 mg. |
| Vitamin A | 25,000 U.S.P. Units |
| Vitamin D | 1,000 U.S.P. Units |

**have confidence in the preparation you prescribe — specify "ARMOUR"**

**ARMOUR** *Laboratories*

**HEADQUARTERS FOR MEDICINALS OF ANIMAL ORIGIN • CHICAGO 9, ILLINOIS**

# ORAL ANDROGEN THERAPY

## ...via Nature's Hypodermic

*"Convenience at practically no sacrifice in effectiveness" sums up the many advantages of oral androgen therapy with "nature's hypodermic" . . . mucosal absorption. Mucosal administration of VANTOSTOL-M BUCCAL TABLETS (methyl testosterone) is highly acceptable to most patients because this form of therapy is easily administered, convenient—and eliminates the fear of injection—ideal for supplemental therapy too.*

VANTOSTOL-M BUCCAL TABLETS have the same indications in both male and female as parenteral testosterone, and are especially useful when moderate dosage is adequate for control and maintenance.

VANPELT & BROWN, Inc., Richmond, Virginia

VANTOSTOL (testosterone) crystalline is also available in the following dosage forms in multiple dose vials.

10 cc.—in aqueous suspension, 10 mg. per cc.
10 cc.—in aqueous suspension, 25 mg. per cc.
10 cc.—in vegetable oil, 10 mg. per cc.
VANTOSTOL-P in vegetable oil—10 cc.
(25 mg. testosterone propionate per cc.)

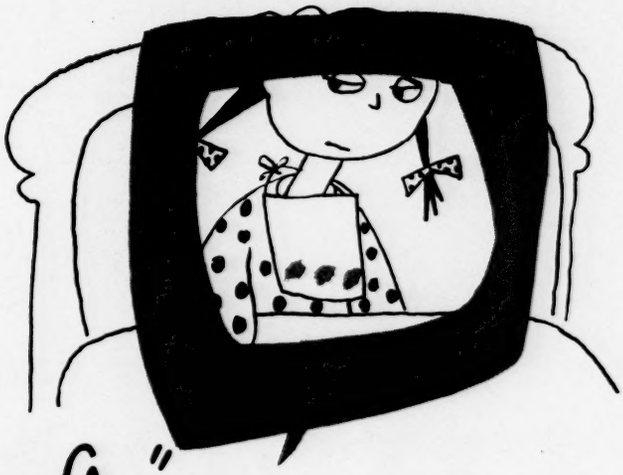
**DOSAGE:**

Five to 20 mg. in divided daily doses.

**SUPPLIED:**

Buccal Tablets (5 mg. methyl testosterone). Buccal Tablets (10 mg. methyl testosterone). Both supplied in bottles of 30 and 100.

**VANTOSTOL-M**
**BUCCAL TABLETS**



# After "T & A"—

■ Aspergum presents the analgesic agent topically, at the site of the pain.

■ Chewing aids removal of tissue waste products, gently stimulates the muscles of deglutition, encourages an earlier return to a full diet—convalescence is hastened.

■ Aspergum also provides a prolonged mild, general analgesia and antipyresis in children. It tastes good—children chew it gladly.

## aspergum®

3½ grains of acetylsalicylic acid per tasty tablet—a dosage and form uniquely fitted to childhood requirements. Promoted ethically.

*WHITE LABORATORIES, INC.,*
*Pharmaceutical Manufacturers, Newark 7, N. J.*


# twice as effective

More nearly complete relief of symptoms associated with hay fever and other allergies can now be provided with Pulvules

This new preparation combines 25 mg. of the antihistaminic 'Histadyl' (Thenylpyramine, Lilly) with 12.5 mg. of the powerful sympathomimetic 'Clopane Hydrochloride' (Cyclopentamine Hydrochloride, Lilly). Clinical observations have revealed that these two drugs are synergistic and their combination is at least twice and often three times as effective as that of 'Histadyl' administered alone.

Ideal for daytime use, Pulvules 'Hista-Clopane' offer greater therapeutic effect with virtually no sedation or stimulation. The average adult dose of Pulvules 'Hista-Clopane' is one or two pulvules after each meal and at bedtime. When indicated, a fifth dose may be taken nocturnally.

*'Hista-Clopane' (Thenylpyramine and Cyclopentamine, Lilly)

ELI LILLY AND COMPANY • INDIANAPOLIS 6, INDIANA, U.S.A.

Complete literature on Pulvules 'Hista-Clopane' is available from your Lilly medical service representative or will be forwarded upon request.

The American Journal of Medicine

VOL. IX AUGUST, 1950 NO. 2

# Editorial

## Body Water

THE importance of water in the economy of the body is often forgotten. Scarcely a chemical reaction in the body can proceed without it. The functioning of every cell depends upon the proper concentration of water. Since water is the medium for the physiologic exchange of substances throughout the body, the nutrition of every cell depends upon its unimpeded movement.

It is not surprising that a measure of the total amount of water in living man has long been sought. Measurements of total water carried out simultaneously with estimations of extracellular water would permit calculation of the amount of water inside the cells, about which little is known. The better the estimate of normal body-water content and of the proportion of water in the various body compartments, the better would be our understanding of the disturbances of water and electrolyte balance in cardiac, renal and hepatic disease, which in turn would lead to more exact therapeutic procedures. The dehydrated patient is another case in point. The more accurately one can predict the amount of fluid and kind of electrolyte needed, the more rapidly can replacement therapy proceed.

The problem was to find an innocuous substance which would distribute evenly throughout the water of all tissues of the body within a reasonable time and be measurable when it was so diluted. Von Hevesy and Hofer succeeded for the first time in 1934 by the oral administration of deuterium oxide (heavy water) to a single subject. Recently, tritium oxide (radioactive heavy water) and deuterium oxide have been given intravenously to measure body water. The methods involved in the analysis of deuterium and tritium oxide are accurate but are tedious and costly and few measurements have consequently been made.

Development of a relatively simple chemical method for measuring body water by the dilution of antipyrine has permitted examination of the range of proportion of water in the human body in eighty-two normal individuals. Normal men ranged from 40 to 68 per cent body water, with an average of 53 per cent. Normal women ranged from 30 to 53 per cent body water, with an average of 45 per cent. The range as well as the low average figure differed somewhat from previous notions of body water content. The data were, however, in essential agreement with observations made by Behnke and his associates in 1942 on the specific gravity of the body in ninety-nine normal men. Specific gravity of the body as a whole is the resultant of the mixture of fat of low density and of the fat-free tissues of high density. They calculated the results in terms of the amount of body fat because that was their interest at the time. They could just as easily have calculated body water since the figure for specific gravity is simply an indication of the proportion of water and fat in the body. Recently this group has measured both the specific gravity and body water by antipyrine in a group of eighty individuals. The agreement

for the figures for total body water by both methods was surprisingly good. The results obtained by dilution of antipyrine are also in general accord with those obtained by dilution of deuterium oxide as well as with the measurement of specific gravity recalculated in terms of body water. Another substance (N-acetyl 4-amino-antipyrine) has been found which distributes through the same volume as antipyrine within the experimental error. That three substances, deuterium oxide, antipyrine and N-acetyl-4-amino-antipyrine are diluted to the same extent in the body; that some of these are in agreement with desiccation studies in animals; and finally, that all three volumes of dilution agree closely with the volume of water calculated from the specific gravity of the body, lend confidence to the belief that any one of them is a measure of total body water within the limits of error of the method chosen.

From the measurement of body water by antipyrine and body fat from specific gravity in the same individuals another interesting figure can be calculated, namely, the water content of "lean body mass" (fat-free tissue). This figure was found to be quite constant, averaging 71.8 per cent, with a standard deviation of 3 per cent. This constancy of the water content of defatted tissue has been demonstrated for many other animal species as well. The result of these studies clearly demonstrates that fat is the great variable in body composition. It seems fair, therefore, to conclude that the proportion of water in the human body depends chiefly on the proportion of fat—the more fat the less water.

It would be highly desirable to study the degree of hydration of lean body mass in disease and in age. But since the total amount of water in the body depends to a much greater degree upon the amount of fat than upon the degree of hydration of the tissues, an attempt to do this appears to be out of the question until a direct method for measurement of body fat becomes available. This fact becomes clear from the observation that even obviously edematous individuals may fall within the normal range of proportion of body water. Thus an obese person with considerable accumulation of edema may still have a smaller percentage of body water than a lean normal person.

The low values obtained for total body water by the new methods have made it necessary to scrutinize carefully those obtained for the extracellular compartment by the dilution of such substances as bromide, thiocyanate, chloride or sodium. Values obtained from the dilution of these substances appear, in the light of the low figures for total body water, too large to be considered correct. Inulin has recently been shown to give a more reasonable measure of extracellular fluid in that it distributes through a much smaller volume of body fluid. Use of inulin for this purpose involves certain serious technical difficulties but enough measurements have been made with it to lead to the conclusion that the extracellular water averages roughly 15 per cent body weight, and intracellular water 40 per cent body weight. Of the total amount of water in the body one-third is extracellular, two-thirds intracellular. It is also clear from these figures that a large proportion of chloride and sodium is intracellular, perhaps a third of the total amount in the body.

Under these circumstances it becomes idle to speak of "chloride or sodium space" since the concentration of that portion of electrolyte which is outside the confines of the extracellular space is unknown. One had perhaps best consider the dilution of bromide as a measure of total chloride in the body and the dilution of radiosodium as a measure of total sodium. This concept does not suggest that knowledge of the degree of dilution of bromide or of radiosodium is any the less important in arriving at an understanding of physiologic and pathologic shifts of fluid and electrolytes in the body. It means, simply, that these shifts may take place without close regard for anatomically considered extra- and intracellular spaces.

J. Murray Steele, M.D.
*New York University Research Service, Goldwater Memorial Hospital, New York*

# Clinical Studies

## A Method for the Evaluation of the Effects of Drugs on Cardiac Pain in Patients with Angina of Effort*

### *A Study of Khellin (Visammin)*

THEODORE GREINER, M.D.,† HARRY GOLD, M.D., MCKEEN CATTELL, M.D., JANET TRAVELL, M.D., HYMAN BAKST, M.D., SEYMOUR H. RINZLER, M.D., ZACHERY H. BENJAMIN, M.D., LEON J. WARSHAW, M.D., AUDRIE L. BOBB, M.D., NATHANIEL T. KWIT, M.D., WALTER MODELL, M.D., HAROLD H. ROTHENDLER, M.D., CHARLES R. MESSELOFF, M.D. *and* MILTON L. KRAMER, M.D.

*New York, New York*

THE compound dimethoxy-methyl-furano chromone, better known as khellin, was isolated in pure form in 1930 by Fantl and Salem[1] from the seeds of Ammi Visnaga, a plant especially common in the Eastern Mediterranean area. This material received little attention until 1946 when Anrep and a group of collaborators explored its action and behavior in a series of pharmacologic and clinical investigations. They found that this compound, in small doses, possessed the property of relaxing smooth muscle of a variety of structures. The reader may refer to the paper by Anrep, Kenawy and Barsoum[2] for references to the most important publications on khellin up to April, 1949.

The effect of khellin on cardiac pain in coronary artery disease has received special attention.[2–4] In a recent paper[2] based on observations in 250 patients with coronary artery disease and the angina of effort or decubitus, Anrep, Kenawy and Barsoum concluded that khellin given by mouth or by intramuscular injection was highly effective in abolishing the pain or reducing the frequency and severity of the attacks in 90 per cent of the patients. That seemed a remarkable record for a drug against the pain of coronary artery disease.

The present study‡ was undertaken for the purpose of obtaining further evidence on the utility of khellin for the control of cardiac pain in patients with angina of effort. Of special importance is the application of a new method for securing facts, which offers the greatest freedom from distortion by innumerable factors affecting patients' statements on cardiac pain[5] and which supplies data accessible to valid statistical analysis.

#### METHOD

The observations were made on a group of thirty-nine patients with coronary artery disease and the angina of effort. These were selected from a case load of approximately 1,500 cardiac patients in active attendance at our cardiac clinics. The basis for the selection was unequivocal evidence of coronary artery disease; pain, substernal, epigastric or interscapular, showing typical radiation, brought on by exertion, and subsiding fairly promptly with rest;

‡ The authors are indebted to Dr. Melvin Moore for his generous assistance.

* From the Department of Pharmacology of Cornell University Medical College, the Cardiovascular Research Unit of the Beth Israel Hospital, and the Cardiac Service of the Hospital for Joint Diseases, New York, N. Y.
† Fellow of the National Institute of Health.

also the fact that the patient was able to distinguish the typical anginal pain from a wide variety of other pains in the chest and arms.

The characteristics of the group are summarized in Table 1. It may be noted that all the common etiologic factors are represented. Their ages range between forty-nine and seventy-eight. Of the entire group, 26 per cent were females and 74 per cent males. An abnormal electrocardiogram was present in 74 per cent and 41 per cent had suffered one or more attacks of coronary thrombosis. These patients were all ambulant and the majority engaged in some kind of work or occupation. The table shows a rough classification of the severity of the anginal problem, chiefly on the basis of the degree to which pain interfered with their capacity to carry on. It may be noted that 33 per cent of the patients were classified as mild (1+). These were usually able to engage in light work without difficulty but exceeded the limits of their tolerance sufficiently often to make it necessary for them to seek treatment for the angina of effort. Of the group, 16 per cent were classified as severe (3+). These were virtually incapacitated by the attacks of cardiac pain. The remaining 51 per cent were classified as moderate (2+) and included a fairly wide range of degrees of limitation in physical capacity. It seemed desirable to include these various degrees of coronary artery disease in the study for a satisfactory evaluation of a supposed coronary vasodilator in order to secure evidence concerning the utility of the agent that may be applicable to angina of effort as it is commonly encountered.

Two materials were compared in this study: coated tablets of lactose and tablets containing 51 mg., in others 31 mg. of khellin. The khellin and placebo tablets were indistinguishable in color, size or shape. They were dispensed at the time of a clinic visit and in sufficient quantity to last the one- or two-week period between clinic visits. The dosage of khellin was essentially similar to that given by others[2] and was either approximately 50, 100 or 150 mg. daily. Most of the patients received the larger doses, as one tablet two or three times a day. As will be shown presently, this dosage is in the range which gives rise to some unpleasant reactions.

The data relating to the effect of the agents were obtained from a "daily report card." Each patient received one or more of these cards at each clinic visit with instructions for its use. It may be seen that the patient is asked four simple questions: From the standpoint of cardiac pain, was the day the same as usual, unusually bad, exceptionally good or one with no pain at all? The answer was made daily at bedtime and the notation required was a cross mark in the appropriate space on the card. We learned in the course of the study that with experience in the use of the card the quality of the answers improved, but in the majority there was little difficulty from the very start since the questions made negligible demands on the patient's intelligence, judgment and memory. The patient returned the "daily report card" at each clinic visit. We took advantage of the clinic visits to review with patients the pattern of the cardiac pain as distinguished from their other pains or discomforts and to keep them alert to the fact that the questions on the card referred to cardiac pain of the particular day and not of others.

"DAILY REPORT CARD" FOR SECURING DATA ON CARDIAC PAIN IN PATIENTS WITH ANGINA OF EFFORT

BRING THIS CARD TO CLINIC NEXT VISIT

How much pain in the heart did you have each day?

| Day of the Week | Same Heart Pain as Usual | Less Heart Pain Than Usual—Good Day | More Heart Pain Than Usual—Bad Day | No Heart Pain at All |
|---|---|---|---|---|
| Monday | | | | |
| Tuesday | | | | |
| Wednesday | | | | |
| Thursday | | | | |
| Friday | | | | |
| Saturday | | | | |
| Sunday | | | | |

Before going to bed, each day, write a mark (X) in the space that describes your heart pain for the entire day.

The work was carried out by a team of physicians in the clinic, all familiar with the plan and with their part in its operation. One person received the "daily report cards," decided on changes in dosage and dispensed the supply of tablets with directions for their

TABLE I

CHARACTERISTICS OF PATIENTS WITH ANGINA OF EFFORT USED IN THIS INVESTIGATION

| Patient | Age | Diagnosis | Severity of Angina | Electrocardiogram + (abnormal) 0 (normal) |
|---|---|---|---|---|
| 1 | 58 | Arteriosclerosis, enlarged heart, coronary sclerosis, coronary thrombosis, diabetes | 3+ | 0 |
| 2 | 68 | Arteriosclerosis, coronary sclerosis, sclerotic aorta, coronary thrombosis | 2+ | + |
| 3 | 67 | Arteriosclerosis, hypertension, coronary thrombosis | 2+ | + |
| 4 | 72 | Arteriosclerosis, hypertension, coronary sclerosis | 2+ | + |
| 5 | 73 | Arteriosclerosis, coronary sclerosis, coronary thrombosis | 3+ | + |
| 6 | 63 | Arteriosclerosis, enlarged heart, coronary sclerosis | 2+ | + |
| 7 | 63 | Luetic, aortic insufficiency, arteriosclerosis, enlarged heart, hypertension, dilated aorta | 1+ | + |
| 8 | 53 | Arteriosclerosis, coronary sclerosis, complete heart block | 2+ | + |
| 9 | 52 | Arteriosclerosis, enlarged heart, dilated aorta | 2+ | + |
| 10 | 58 | Arteriosclerosis, enlarged heart, coronary sclerosis, coronary thrombosis, dilated aorta | 1+ | + |
| 11 | 78 | Arteriosclerosis, enlarged heart, coronary sclerosis, coronary thrombosis, hypertension | 2+ | + |
| 12 | 49 | Arteriosclerosis, coronary sclerosis, coronary thrombosis | 2+ | 0 |
| 13 | 64 | Luetic, enlarged heart, aortic insufficiency | 1+ | + |
| 14 | 55 | Arteriosclerosis, coronary sclerosis, coronary thrombosis | 1+ | 0 |
| 15 | 61 | Arteriosclerosis, coronary thrombosis | 3+ | + |
| 16 | 60 | Arteriosclerosis, enlarged heart, coronary sclerosis, coronary thrombosis | 3+ | + |
| 17 | 71 | Arteriosclerosis, enlarged heart, sclerotic aorta | 1+ | + |
| 18 | 59 | Arteriosclerosis, coronary sclerosis, coronary thrombosis | 2+ | + |
| 19 | 75 | Arteriosclerosis, enlarged heart, coronary sclerosis, coronary thrombosis | 2+ | + |
| 20 | 65 | Arteriosclerosis, hypertension, coronary sclerosis | 1+ | + |
| 21 | 59 | Arteriosclerosis, hypertension, enlarged heart, coronary sclerosis | 1+ | + |
| 22 | 65 | Arteriosclerosis, coronary sclerosis | 2+ | 0 |
| 23 | 50 | Arteriosclerosis, enlarged heart, coronary sclerosis, coronary thrombosis | 1+ | + |
| 24 | 66 | Arteriosclerosis, enlarged heart, dilated aorta, coronary thrombosis | 2+ | + |
| 25 | 52 | Hypertension, enlarged heart | 2+ | 0 |
| 26 | 74 | Arteriosclerosis, enlarged heart, calcified aorta | 1+ | + |
| 27 | 59 | Arteriosclerosis, enlarged heart, dilated aorta, hypertension | 2+ | 0 |
| 28 | 72 | Arteriosclerosis, coronary sclerosis | 2+ | + |
| 29 | 65 | Arteriosclerosis, hypertension, coronary sclerosis, diabetes | 2+ | + |
| 30 | 68 | Arteriosclerosis, hypertension, enlarged heart, dilated aorta | 2+ | + |
| 31 | 63 | Arteriosclerosis, hypertension, diabetes | 1+ | + |
| 32 | 58 | Arteriosclerosis, hypertension, enlarged heart, coronary sclerosis, coronary thrombosis | 3+ | + |
| 33 | 70 | Arteriosclerosis | 1+ | 0 |
| 34 | 56 | Arteriosclerosis, hypertension, enlarged heart, coronary sclerosis, coronary thrombosis | 2+ | 0 |
| 35 | 70 | Arteriosclerosis, hypertension enlarged heart, coronary sclerosis | 1+ | 0 |
| 36 | 67 | Arteriosclerosis, hypertension | 1+ | 0 |
| 37 | 73 | Arteriosclerosis, hypertension, enlarged heart | 1+ | 0 |
| 38 | 73 | Arteriosclerosis, enlarged heart, aortic insufficiency, coronary thrombosis | 2+ | + |
| 39 | 55 | Luetic, hypertension, enlarged heart | 2+ | 0 |

use. He knew what the patient had been taking but this knowledge played no part in the record of the results, for his function was neither to question patients regarding the effect of the tablets nor to record judgment; he merely assembled and filed "daily report cards."

The other participating physicians were examiners. They made a fairly complete physical examination and recorded the results on a special chart provided with rubrics on history and physical findings. They also recorded an "interval-evaluation" of the cardiac pain, as unchanged, better or worse, in relation to the patient's habitual status. The "interval-evaluation" was made by skilled questioning under conditions of the "double blind test" in which neither the physician nor the patient knew at the time whether the evaluation related to the placebo or khellin.* The method was essentially similar to that employed in our study of the xanthines.[5] It should be mentioned that no attempt was made to decide the reason for the change in pain. The "interval-evaluation" was a statement of fact as accurate as possible. The "interval-evaluation" was not an essential part of the study but was included for the purpose of comparing the merits of the "daily report card" with the "interval-evaluation" as systems for securing the facts concerning the effect of drugs on pain of the angina of effort.

## RESULTS

Early in the course of the study we found ourselves eager for an impression of the kind of answer the comparison was likely to yield and so an analysis was made of observations in the first few weeks. It was based on data secured in nineteen patients, representing the reports on 243 days of khellin and 291 days of the placebo. The results are summarized in Table II. Khellin appeared quite superior to the placebo in that the number of "bad days" for khellin was about half as many, the number of "good days" about twice as many, and the number of days with "no pain" four times as many as in the case of the placebo. This preliminary analysis was made before the study had progressed sufficiently to make it possible to take advantage of all the details of a balanced design for the comparison of the two agents. Of the nineteen patients, only nine had received both agents, six had received only placebo and four had received only khellin.

TABLE II

PRELIMINARY DATA IN COMPARISON OF KHELLIN AND PLACEBO ON CARDIAC PAIN BY THE METHOD OF THE "DAILY REPORT CARD" IN NINETEEN PATIENTS WITH ANGINA OF EFFORT

| Agent | Total No. Days Reported | Percentage of Days in Which Cardiac Pain Was Reported as | | | |
|---|---|---|---|---|---|
| | | Unchanged (same)* | Increased (bad day) | Reduced (good day) | Absent (no pain) |
| Khellin | 243 | 52 | 13 | 23 | 12 |
| Placebo | 291 | 61 | 23 | 13 | 3 |

* Terms in parentheses used on "report card."

In accordance with the plan the study was continued and by the time of its completion it included thirty-nine patients and the data represented nearly 1,500 days reported with each of the two agents. All patients received both khellin and placebo tablets. The two agents were administered in courses lasting from two to four weeks, the average for the khellin, 2.9 weeks, and for the placebo, 3.0 weeks. There were in all seventy-seven courses of khellin and seventy-four of the placebo. The average duration of treatment with both placebo and khellin was 11.5 weeks. The courses were alternated in each patient. The procedure was further randomized by starting a course of treatment during any particular clinic session with placebo in one-half of the patients and with khellin in the other half. The results are summarized in Table III. In Group I all thirty-nine patients were included and the data represented nearly 1,500 days reported with each of the two

* Visammin has been recognized by the Council on Pharmacy and Chemistry as the generic name for the compound [*J. A. M. A.*, 141: 26, 1949]. The material used in this study was supplied by Smith, Kline & French Labs., Phila., who state that the preparation is a mixture of approximately 75 per cent khellin and 25 per cent visnagin (assayed as khellin-equivalent). In this paper, therefore, the doses of khellin, as stated, represent this mixture of furanochromones.

agents. In Group II twelve patients whose competence in using the "report card" was not altogether satisfactory were eliminated. The remaining twenty-seven patients represented in this analysis embraced reports on somewhat more than 1,000 days for each of the two agents. Under Group III are summarized the data in the same twenty-seven patients but here the reports for the first three days of khellin and the reports for the first seven days of the placebo following khellin are omitted. These omissions were made because of the possibility that khellin might not show its optimum effects until several days of cumulation, while in the case of the placebo the reports of the first seven days might bear the traces of the persistence of khellin action.[2,6]

TABLE III
COMPARISON OF KHELLIN AND PLACEBO ON CARDIAC PAIN BY THE METHOD OF THE "DAILY REPORT CARD" IN PATIENTS WITH ANGINA OF EFFORT

| Groups | Agent | No. Days Reported | Percentage of Days in Which Cardiac Pain Was Reported as | | | |
|---|---|---|---|---|---|---|
| | | | Unchanged (same)* | Increased (bad day) | Reduced (good day) | Absent (no pain) |
| (I) | | | | | | |
| All 39 patients. | Khellin | 1489 | 41.6 | 17.2 | 20.9 | 20.3 |
| | Placebo | 1463 | 42.8 | 17.2 | 21.8 | 18.2 |
| (II) | | | | | | |
| The 27 patients whose use of the "daily report card" was faultless | Khellin | 1049 | 41.3 | 14.8 | 21.2 | 22.7 |
| | Placebo | 1021 | 46.2 | 15.5 | 20.3 | 18.0 |
| (III) | | | | | | |
| The above 27 patients whose records were adjusted for khellin cumulation and excretion | Khellin | 899 | 40.6 | 15.5 | 21.9 | 23.0 |
| | Placebo | 827 | 46.9 | 16.8 | 20.7 | 15.6 |

* Terms in parentheses used on "report cards."

Comparison of the results in Tables II and III provides a striking demonstration of the danger of inadequate data. Contrary to the indications in the results with the small unbalanced series of observations, the evidence from the complete results shows that the number of days in which pain was unchanged, increased, diminished or absent were the same for khellin as for lactose. The higher value for the category of days with "no pain" in the case of khellin is probably due to the fact that contributions of data to this column were made by only fifteen of the patients, and 80 per cent of the answers were supplied by only six patients.

The data in Table III fail to distinguish one patient from another and could mask pharmacologic effects of khellin in any particular individual. Accordingly, the facts were rearranged to compare khellin with the placebo in terms of the number of patients in whom one or the other agent showed "superior" effects. From the total number of days reported by each patient, the percentage of "bad days," "good days" and "days without pain" was determined in the case of each of the two agents. The score for each patient was determined in the manner shown by the following example: When, as in one patient, 42 per cent of the khellin-days and 14 per cent of the placebo-days were "bad," the difference between the two was taken to represent a 28 per cent "advantage" for placebo; when 11 per cent of the khellin-days and 3 per cent of the placebo-days were "good," it was taken to represent an 8 per cent "advantage" for khellin; when 38 per cent of the khellin-days and 51 per cent of the placebo-days were "without pain," it was taken to represent a 13 per cent "advantage" for placebo; the two values, 28 and 13 per cent, add up to a 41 per cent "advantage" for placebo; and when the 8 per cent "advantage" for khellin is subtracted, it leaves a "net advantage" of 33 per cent for placebo. When the "net advantage" for one or the other agent exceeded 10 per cent, the patient was placed in a group labelled "superior" for the particular agent. In this way it became possible to classify the patients into three groups, namely, those in whom khellin was "superior," those in whom placebo was "superior," and those in whom the two agents were "equal." The assumption was made that both agents exert the effect of suggestion; and if khellin had, in addition, a beneficial pharmacologic action in some of the patients, the number of patients in the khellin-"superior" group would be

significantly larger. The results are summarized in section A of Table IV. It may be seen that khellin was "superior" in thirteen, placebo "superior" in twelve and that the two agents were "equal" in the remaining fourteen of the patients.

to obtain the percentage of "bad days" for khellin. The data on the placebo were treated similarly. The same procedure was followed in the case of the "good days" and "days without pain" and for the other two groups (Groups II and III of Table IV). The

TABLE IV

COMPARISON OF KHELLIN AND PLACEBO ON CARDIAC PAIN BY THE METHOD OF THE "DAILY REPORT CARD" IN EACH OF THIRTY-NINE PATIENTS WITH ANGINA OF EFFORT

| A | | B | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Groups | No. Patients | Total No. Days Reported | | Percentage (Average) of Days in Which Cardiac Pain Was Reported as | | | | | |
| | | | | Increased (bad day) | | Reduced (good day) | | Absent (no pain) | |
| | | Khellin | Placebo | Khellin | Placebo | Khellin | Placebo | Khellin | Placebo |
| I. Khellin "superior" | 13 | 495 | 505 | 7 | 17 | 24 | 19 | 25 | 16 |
| II. Placebo "superior" | 12 | 347 | 433 | 33 | 20 | 20 | 31 | 12 | 17 |
| III. Khellin and placebo "equal" | 14 | 647 | 525 | 17 | 15 | 19 | 17 | 21 | 20 |

TABLE V

COMPARISON OF KHELLIN AND PLACEBO ON CARDIAC PAIN BY THE METHOD OF "INTERVAL-EVALUATION" IN A GROUP OF TWENTY-SEVEN PATIENTS WITH ANGINA OF EFFORT

| Drug | Total No. of "Interval-evaluations" (Clinic Visits) | Percentage of "Interval-evaluations" in Which the Pain of the Anginal State Was Judged as | | | |
|---|---|---|---|---|---|
| | | Unchanged (interval—same) | Increased (interval—bad) | Diminished (interval—good) | Absent (interval—no pain) |
| Khellin | 127 | 47.3 | 11.0 | 41.7 | 0 |
| Placebo | 132 | 50.5 | 7.6 | 40.9 | 0 |

The data were then arranged in an endeaver to learn whether a difference between the two agents might be revealed by the degree of "superiority" in the khellin group and the placebo group. Accordingly, the total number of "bad days" for khellin in the thirteen patients of the khellin-"superior" group (Group I of Table IV) were added up and divided by the total number of khellin-days reported by those patients

results are shown in section B of Table IV. It may be seen that the degree of "superiority" expressed in this way is similar for Groups I and II. If one examines the values in pairs (khellin and placebo) across the Table (section B) and considers a "disadvantage" for one agent as an "advantage" for the other, the values representing the degree of "superiority" in the two groups are as follows: 24 per cent for the khellin-

"superior" group and 29 per cent for the placebo-"superior" group.

### "INTERVAL-EVALUATION" VERSUS "DAILY REPORT CARD"

Table v presents a summary of the comparison of khellin and the placebo in the group of twenty-seven patients in terms of data collected by the more conventional method, namely, an evaluation of the patient's status with respect to the angina of effort in the intervals between clinic visits. As stated previously, the judgment was made at each clinic visit by the examiner without knowledge at the time whether the evaluation related to khellin or placebo. The treatment of these data was similar to that of the data supplied by the "daily report card" method in the same twenty-seven patients shown in Table III (group II). In this instance the two methods yielded substantially similar answers, although the result in the case of the "interval-evaluation" method was less decisive, one pair of values being out of line with the others, showing a more frequent increase in pain for khellin (11 per cent) than for the placebo (7.6 per cent).

Table VI presents a summary of the experience of each patient with both agents. It shows the comparison of khellin and the placebo in each of all thirty-nine patients in terms of the data supplied by the "interval-evaluation" method. The treatment of these data was similar to that of the data supplied by the "daily report card" method which is shown in Table IV. In this comparison different answers emerged by the two methods; the "daily report card" method suggests that the placebo is equal to khellin, while the "interval-evaluation" method suggests the placebo to have considerably more value than khellin. It is unlikely that khellin increases anginal pain. It is also safe to assume that the "interval-evaluation" method has nothing like the precision of the "daily report card" method when applied to the observations on the same sample of thirty-nine patients treated during a period of approximately three months.

TABLE VI

COMPARISON OF KHELLIN AND PLACEBO ON CARDIAC PAIN BY THE METHOD OF "INTERVAL-EVALUATION" IN EACH OF THIRTY-NINE PATIENTS WITH ANGINA OF EFFORT

| A | | B | | | | | |
|---|---|---|---|---|---|---|---|
| Category | No. of Patients | Total No. of "Interval-evaluations" (Clinic Visits) | | Percentage (Average) of "Interval-evaluations" in Which the Pain of the Anginal State Was Judged as | | | |
| | | | | Increased (interval—bad) | | Diminished (interval-good) | |
| | | Khellin | Placebo | Khellin | Placebo | Khellin | Placebo |
| Khellin "superior" | 11 | 54 | 57 | 2 | 7 | 70 | 40 |
| Placebo "superior" | 20 | 97 | 107 | 21 | 7 | 26 | 49 |
| Khellin and placebo approximately equal | 8 | 29 | 26 | 0 | 0 | 10 | 19 |

### COMPARISON OF KHELLIN AND PLACEBO ON BLOOD PRESSURE

The systemic blood pressure was recorded during the vast majority of clinic visits. The pressure was taken on the same arm with the patient resting in a chair. The results are summarized in Table VII. There were in all thirty-nine patients a total of 300 readings, approximately an equal number with khellin and the placebo, and an aver-

age of approximately four readings a patient during both the khellin and placebo periods. The diagnosis of hypertension had been made prior to the present study in about 40 per cent of the patients. The basis was a blood pressure of 150/90 or higher in most of the readings. It may be noted that the average blood pressures were similar during the khellin and placebo periods in both groups, those with and those without hypertension.

### TOXIC EFFECTS OF KHELLIN

In the course of this study thirty-five of the thirty-nine patients reported unpleasant symptoms at one time or another which they ascribed to the medication. The cause of these symptoms was not always certain. Most of the subjects were along in years and in poor health, and in these symptoms referable to the gastrointestinal tract and central nervous system are fairly common. Unpleasant symptoms in thirteen of the patients (about 33 per cent) could be assigned as side actions or toxic actions of the khellin in the doses we used. Among these, two refused to continue the drug because of such symptoms as vertigo, drowsiness, unrest and impaired power of concentration. The drug had to be discontinued in two patients because of anorexia, nausea, vomiting and epigastric pain which persisted even with reduced dosage. Milder discomforts referable to the gastrointestinal or central nervous system were reported by nine other patients during the period on khellin which were not observed during the use of the placebo. The remaining twenty-two patients, who ascribed a variety of unpleasant symptoms to the new medication, complained of the same symptoms during the courses of placebo and khellin. The experience with this group of thirty-nine patients with the angina of effort indicates, therefore, that while oral daily doses of khellin of the order of 100 or 150 mg. occasionally give rise to pronounced side reactions, the vast majority tolerate such doses for several weeks with little or no unpleasant reaction. It is worth noting that by the conventional method of study in which only the drug in question is employed the conclusion concerning toxic effects of khellin would have been misleading. It was from the comparison of khellin with the placebo that the fact emerged that the majority of unpleasant symptoms during the use of khellin had no relation to the drug.

TABLE VII
COMPARISON OF KHELLIN AND PLACEBO ON BLOOD PRESSURE

| Group | Khellin | | Placebo | |
|---|---|---|---|---|
| | Average Blood Pressure | No. Readings (Clinic Visits) | Average Blood Pressure | No. Readings (Clinic Visits) |
| All 39 patients | 152/83 | 152 | 157/85 | 148 |
| 16 patients with hypertension | 175/94 | 67 | 177/95 | 72 |
| 23 patients with normal blood pressure | 134/75 | 85 | 139/77 | 76 |

### COMMENTS

A noteworthy aspect of the experience with drugs for the control of pain in patients with the angina of effort is the lack of accord among different observers concerning their value. Attention was called to this situation in the paper by Gold et al.[5] in connection with their study on the utility of the xanthines, theobromine and aminophylline, in patients with cardiac pain. In that study and in the study by Evans and Hoyle[7] it could not be proved that the xanthines by oral administration exert any beneficial effects in the routine treatment of patients with coronary disease and cardiac pain. Yet the literature is replete with publications to the effect that these compounds are valuable agents for the treatment of pain in the angina of effort. In the paper published in 1937 by Gold et al.[5] the belief was expressed that few were the patients with angina of effort who escaped a course of treatment with the oral xanthines at one time or another. In the long period of years which have elapsed since the above publication and the one by Evans and Hoyle,[7] our observations fail to detect that the liberal

use of oral xanthines has undergone any material change. We are inclined to believe that the survival qualities of these and other agents of doubtful value in the angina of effort receive most of their strength from the urgent need of patients for relief and the want of effective measures with which to supply it. However, part of the trouble probably lies in the fact that the evaluation of drugs for the control of cardiac pain presents a problem of unusual difficulty, that experience indicating beneficial effects has on its side the force of suggestion, and that the methods employed in the investigation of these agents may not have been sufficiently free of defects to carry complete conviction.

Evaluations have been made in a variety of ways. Some of the more serious attempts at scientific evaluations have become involved in the use of a possible objective equivalent to the symptom, pain. There are the studies of Levy et al.[8] in which the value of aminophylline in the angina of effort was deduced from changes in the electrocardiogram, interpreted as the lifting of cardiac anoxia. There are risks in the assumption that alterations in the response of the T-wave to artificially induced anoxia by the use of an alleged coronary dilator represent a change in the coronary circulation, or one of sufficient magnitude to enhance perceptibly the patient's capacity to carry on without pain. Also, in our experience a change in T-wave often may be induced in patients with coronary disease in the absence of pain, and pain may be often induced in the absence of a significant change in the T-wave.

Riseman et al.[9] and others have endeavored to evaluate such agents by means of pain as an end point, but have used for this purpose a special exercise tolerance test. Such tests may indeed provide information concerning the effectiveness of one agent as compared with another on the ability to perform work of a special kind under special conditions. The study made with this method in our clinic by Bakst et al.,[10] in which intravenous aminophylline was compared with an intravenous placebo by the "double blind test" on the ability of patients to perform the special task of walking stairs, is a good example of the scientific use of such a method. However, there are reasons for suspecting that values obtained in this way might not apply to the angina of effort in patients functioning in their habitual manner. Wolff and his collaborators[11] have shown that the natural pain experience is not a simple perception but a composite of perception and reaction. The total distress expressed as pain depends not alone on the intensity of the pain perception but on feeling states that may exist or may be aroused by factors associated with the pain perception, such as anxiety, frustration, fear and panic. There is interaction between pain perception and such feeling states, each possessing the power to diminish or intensify the total experience expressed as pain. In the usual exercise tolerance tests in which the exertion is carried out in a special environment under artificial conditions, and with concentration on a particular set of rules, the patient's usual attitude toward his illness may well be erased, leaving little more than the perception of pain as a measure of capacity for exertion. A response to a drug revealed under these conditions might conceivably escape detection in what seems to be a complexity of factors responsible for pain in the ambulant patient with the angina of effort. There is no complete agreement on the elements which give rise to the pain stimulus in coronary disease.[12,13] Also, the mechanisms of the widely differing patterns of angina are not fully understood. There are the patients in whom almost any kind of physical exertion beyond a point causes pain. But in many the design seems more intricate; for example, the patient who has to take several tablets of nitroglycerin between arising in the morning and the end of breakfast but may go through a full day of work, walking about with little or no discomfort; or the patient who is subject to the anginal pain while sitting comfortably in a chair in the evening reading a news-

paper but is free of pain when preoccupied with the day's work which may involve him in emotional outbursts, dashing about and walking several flights of stairs. The specific point which we question is the position that the response to a coronary dilator, detected in an exercise tolerance test as described previously, will necessarily reveal itself in such cases as we have mentioned by an improved capacity to carry on in their habitual way. There is the possibility that in many if not all patients a significant factor which helps to bring on the anginal pain represents an impaired capacity for adjustment, leading either to undue tension in the coronary vessels or unfavorable relationship between cardiac work and coronary flow, and this defect may operate under the stress of certain conditions even when the demand for cardiac work is relatively small or when a drug maintains the coronary vessels in a state of moderate dilatation.

Only experiment can decide this point. As matters stand, the case for the general applicability of the results obtained by electrocardiographic changes or the exercise tolerance test is not sufficiently conclusive. There seems to be no ready escape from dependence on the modality of pain in its natural habitat in exploring drugs for the control of pain of the angina of effort. With any other approach to the problem known at the present time, there will remain the need for filling a gap.

Among the methods which employ, as a measure, the patient's ability to carry on without pain there is the most ancient one, and still the most prevalent, namely, the one in which the patient receives the drug and returns after a week or two with a verbal report on impressions. This is probably evaluation at its worst. There are represented in the conclusions not only a possible pharmacologic action of the particular agent but a number of factors responsible for so-called spontaneous variations in the severity of the anginal state, and the several factors of suggestion such as the taking of a new medicine and the physician's personality and enthusiasm for the new agent.

Others have attempted to gather data by means of a diary system and the use of a placebo. There is the report by Elek and Katz[14] on the effect of papaverine on the anginal syndrome. The patient was required to keep a daily diary covering a period of two weeks for each of the numerous alternating courses of treatment. This was presented to the physician for review at each visit. The record included the daily number of anginal attacks, the duration of each attack, the severity of each attack, the average number of blocks the patient could walk daily without precordial pain and the number of nitroglycerin tablets taken to alleviate severe pain. Other factors taken into account were the patient's reaction to the medication, weather conditions, change in daily activities and emotional upsets. Here the investigator is confronted with an insurmountable tangle of material. To such widely diversified factors there is no way of assigning values which can add up to a single expression concerning the patient's status without more or less arbitrary judgments, and it is unsafe to assume that they are impartial when the physician knows that the record relates in one case to an inert placebo and in another to a supposedly potent agent. In the same investigation the papaverine tablet was three times the size of the placebo and the authors attempted to balance the possible psychologic effect of this difference by informing the patient that a higher concentration of a drug makes a small tablet as potent as a large one. Psychologic factors are probably too complex and subtle to be eliminated by such a device; and when patients receive both large and small tablets, each for a period of two weeks and alternated in as many as sixteen courses, it cannot be decided without experiment to what extent difference in size of tablets influences results.

An analogous issue presented in the report on the xanthines in angina pectoris by LeRoy[15] may be mentioned. He also made

use of a placebo but apparently objected to remaining in the dark about the medication and expressed his view as follows: "In this connection should be mentioned the psychologic attitude of the clinician toward the drug in question. It is just as unfair in seeking a patient's evaluation of a drug to lead him to expect poor results as to lead him to anticipate good ones. I attempted to be as noncommital as possible, but discerning patients may well have seen my enthusiasm for these particular xanthine drugs." An evaluation of the physician's enthusiasm (positive suggestion) on the angina of effort would be a study of some interest in itself but it seems self-evident that the physician's enthusiasm is inadmissible in a scientific experiment for the purpose of seeking out the specific pharmacologic merits of an agent in the control of the angina of effort.

Studies in which a placebo is used commonly fail to take full advantage of this device for securing a decisive answer. The data relating to the placebo are often omitted from the final analysis. For example, in the report by Elek and Katz[14] mentioned above the observation is made that papaverine proved effective in 70 per cent of the patients. However, there is no statement concerning the proportion of patients in whom the placebo proved effective. Also, in the report by Anrep et al.[2] on khellin in which reference is made to the use of a placebo to "eliminate any possible interference of a psychic element," there is no description of the design of the comparison of khellin with the placebo, and their tabulation of results leaves the reader without the information essential for judging the adequacy of the comparison and the significance of any differences which may appear.

The influence of suggestion cannot be eliminated in the study of a drug effect on cardiac pain but its power to confuse the results can be neutralized by the use of an appropriate placebo in a "double blind test" in which the identity of the drug and placebo remains unknown to the patient and physician until the analysis of the data is completed. Such an investigation is perhaps more correctly viewed not as a study of the effect of one particular drug but as a comparison of the effects of two agents, the drug in question and the inert placebo, the difference between the effects of the two representing the pharmacologic effect of the particular drug. In such a comparison the patient is required to distinguish an inert material from the allegedly potent agent by the effect on cardiac pain under conditions which preclude the possibility of their differentiation by any other means such as appearance, taste, color, size or other properties. This was the method employed in the present study.

A noteworthy feature of this study is a new technic devised for securing data on the effect of drugs on the angina of effort in ambulant patients carrying on in their habitual manner. All that is required of the patient is a statement of fact concerning his anginal problem at the end of each day under any one of four headings: "same as usual," "bad day," "good day" and day with "no pain." He records this by a check mark in the appropriate space on a card provided for that purpose. This system has several advantages over the more widely used "interval-evaluation" systems in which a medication is taken for a week or longer and then a judgment is made on the status during this interval. There always remains considerable uncertainty as to the uniformity of the criteria on which such judgment is based. A particularly bad day during a week or two may color the patient's impression of the entire period, so also a few days exceptionally free of pain. It is sometimes difficult to be certain whether or not the judgment is based on the condition of the last day or two. The "daily report card" system is relatively free of these defects. It makes minimum demands on the patient's intelligence and memory. Few are the patients who are unable to state with a fair degree of accuracy at the end of the day how matters have gone with them that day, in such terms as no pain,

very little pain (a good day) or greatly troubled by pain (a bad day). This method provides useful data on days with "no pain" which cannot be secured in long interval-evaluations in which days with and without pain are included in a single judgment. The data secured by the new method are flexible, as shown by the ease with which it was possible to deal with a question which arose after the study was completed, namely, the possibility that the record for khellin might have been impaired by inclusion of the first three days of treatment before sufficient cumulation, and the record for the placebo improved by the inclusion of the first seven days of placebo after a course of khellin which might represent the persistence of khellin activity.

The "daily report card" system supplies a much larger volume of data for analysis, hence it is possible to make a valid comparison of agents on a much smaller number of patients and over a much shorter period of time. This is so because every day counts. In the present study on khellin it provided approximately eight times as much data as the "interval-evaluation" method. This is of special importance in the comparison of drug effects in which a difference may appear. In such a case the observations would be managed in the conventional manner for enumeration data by a contingency table using "treatment" with the placebo or the drug as one attribute and the various categories of effects as the other. The $Chi^2$ would be used as a test of the significance of the difference. All categories of effects might be considered or, in the event of special interest in any one of them, such as "bad day" or "no pain," the number of days in that particular one could be compared with the total days in all the other categories. The large number of units provided by the "daily report card" would clearly facilitate the establishment of a real difference.

In a preliminary report on khellin Rosenman, Fishman and Katz[4] stated that while not all patients benefited from khellin some showed "dramatic responses." We also encountered cases which suggested "dramatic" benefits. For example, in one patient with a record of ninety-eight daily reports, there were 33 per cent "good days" and no "bad days" for khellin as against only 3 per cent "good days" and as much as 6 per cent "bad days" for the placebo; conversely, in another patient with a record of ninety-six daily reports, there were only 19 per cent "good days" and as much as 51 per cent "bad days" for khellin as against 35 per cent "good days" and only 18 per cent "bad days" for the placebo. Such isolated case records may be misleading and, as noted in Table IV, the number of patients who showed what would be regarded as "dramatic responses" to khellin was similar to that for the placebo. The large volume of data supplied by the "daily report card" method provides a means for detecting chance variations unrelated to the drug. At the same time it provides a reliable means for spotting, in a small group of patients, the few in whom a pharmacologic effect of a drug may occur which might be masked in the failure of response by the majority.

The "daily report card" employed in the present study of khellin in angina of effort provides a simple method which can be adapted to a comparison of the effect of drugs on a symptom relating to any organ or system. In this connection a word of caution may be stated to avoid a false sense of security. We have mentioned the fact that this method makes relatively little demand on the patient's intelligence and memory. This should not be taken to imply that the method is safe from error without experience, careful planning and constant vigilance to insure that the patient continues to understand the nature of the questions and answers. The hazards are greater in the study of symptoms that are vague and not easily defined. They are also greater in patients who have numerous symptoms and may be apt to confuse one with another. It may be recalled that in spite of incessant efforts to maintain a sharp

focus on the anginal pain as distinguished from other discomforts, competence in the use of the "daily report card" by nearly one-third of the patients in this study fell short of the high standard that was set. They were either slow in grasping the precise meaning of the questions or were subject to lapses in comprehension or performance. The analysis of data supplied by the "daily report card" system is extremely simple but in studies of this kind one cannot overemphasize the fact that the conclusions can never have more worth than the observations on which they are based.

## SUMMARY AND CONCLUSIONS

1. A new method is described for the comparison of agents in the control of pain of the angina of effort. It makes use of a "daily report card" for securing data.

2. The method is relatively free of the shortcomings of other methods in common use, such as "interval-evaluations," the diary, the T-wave changes in the electrocardiogram and the exercise tolerance test.

3. The method provides the maximum amount of information and supplies data in a form readily accessible to statistical analysis.

4. The method was applied in a comparison of khellin in oral doses of approximately 100 and 150 mg. daily, with lactose in tablets of similar size, shape and color, administered in alternating courses over a period of approximately three months.

5. The results in thirty-nine patients involving the comparison of approximately 1,500 days with each of the two agents show that khellin has no greater effect than lactose in the control of pain of the angina of effort.

6. Sources of error in the use of inadequate data and unbalanced design of study are pointed out.

7. The "daily report card" system employed in this study is applicable to the investigation of the effects of drugs on a symptom involving other organs and systems.

## REFERENCES

1. Fantl, P. and Salem, S. I. Cellol-glucosid. *Biochem. Ztschr.*, 226: 166, 1930.
2. Anrep, G. V., Kenawy, M. R. and Barsoum, G. S. The coronary vasodilator action of khellin. *Am. Heart J.*, 37: 531, 1949.
3. Anrep, G. V., Barsoum, G. S., Kenawy, M. R. and Misrahy, G. Ammi Visnaga in the treatment of the anginal syndrome. *Brit. Heart J.*, 8: 171, 1946.
4. Rosenman, R. H., Fishman, A. P. and Katz, L. N. A preliminary report on the use of khellin in angina pectoris and bronchial asthma. Program of Twenty-Second Scientific Sessions of the American Heart Association, (abstract) p. 43, June 3–4, 1949.
5. Gold, H., Kwit, N. T. and Otto, H. The xanthines (theobromine and aminophylline) in the treatment of cardiac pain. *J. A. M. A.*, 108: 2173, 1937.
6. Anrep, G. V., Barsoum, G. S. and Kenawy, M. R. The pharmacological actions of the crystalline principles of Ammi Visnaga Linn. *J. Pharm. & Pharmacol.*, 1: 164, 1949.
7. Evans, W. and Hoyle, C. The comparative value of drugs used in the continuous treatment of angina pectoris. *Quart. J. Med.*, 26: 311, 1933.
8. Levy, R. L., Bruenn, H. G. and Williams, N. E. The modifying action of certain drugs (aminophyllin, nitrites, digitalis) upon the effects of induced anoxemia in patients with coronary insufficiency. *Am. Heart J.*, 19: 639, 1940.
9. Riseman, J. E. F. and Brown, M. G. Medicinal treatment of angina pectoris. *Arch. Int. Med.*, 60: 100, 1937.
10. Bakst, H., Kissin, M., Leibowitz, S. and Rinzler, S. The effect of intravenous aminophylline on the capacity for effort without pain in patients with angina of effort. *Am. Heart J.*, 36: 527, 1948.
11. Wolff, H. G., Hardy, J. D. and Goodell, H. Studies on pain. Measurement of the effects of morphine, codeine, and other opiates on the pain threshold and an analysis of their relation to the pain experience. *J. Clin. Investigation*, 19: 659, 1940.
12. Wenckebach, K. G. Angina pectoris and the possibilities of its surgical relief. *Brit. M. J.*, 1: 809, 1924.
13. Martin, S. J. and Gorham, L. W. Cardiac pain; an experimental study with reference to the tension factor. *Arch. Int. Med.*, 62: 840, 1948.
14. Elek, S. R. and Katz, L. N. Some clinical uses of papaverine in heart disease. *J. A. M. A.*, 120: 434, 1942.
15. LeRoy, G. V. The effectiveness of the xanthine drugs in the treatment of angina pectoris. x. Aminophylline. *J. A. M. A.*, 116: 921, 1941.

# Pain Patterns in Acute Myocardial Infarction*

JAMES H. BEHRMANN, M.D., HAROLD R. HIPP, M.D. *and* HOWARD E. HEYER, M.D.
*Topeka, Kansas* *Houston, Texas* *Dallas, Texas*

ALTHOUGH the presence of premonitory pain and angina pectoris preceding an episode of acute myocardial infarction has been noted by many authors, relatively little attention has been paid to the possible prognostic significance of the total duration of pain, the location of pain, exact mode of onset, the constancy or intermittency of pain and the complete absence of pain. An analysis of the relationship between the duration and site of occurrence of pain and the mortality rate, and also a delineation of the various modes of onset in acute myocardial infarction form the basis of the present study.

## MATERIAL

One hundred fifty cases of recent myocardial infarction comprise this series. These cases were a series of consecutive hospital admissions for this disease within the period from 1946 to 1948. The data for the study have been obtained from the clinical records; many of the patients have been seen personally by the authors. Most of the patients have had a definite story of chest pain, one or more signs of tissue destruction, such as fever, leukocytosis and increased sedimentation rate, and characteristic electrocardiographic changes. There are a few cases included in which the primary diagnostic evidence was characteristic progressive electrocardiographic changes without signs of tissue necrosis. In these instances progression and regression of the changes have been observed with serial tracings. In thirty-seven cases there was autopsy confirmation of the diagnosis. Because of the stringency of these diagnostic criteria some cases of small myocardial infarction have probably been excluded from this series. In this connection it should be noted that numerous case histories were discarded as unsuitable for inclusion in this series because careful descriptions of the duration and location of the pain or of its mode of onset were not recorded.

The ages ranged from twenty-seven to eighty-four years, the average age being fifty-seven years. The series is weighted with males because a portion of the series was obtained from a hospital of predominantly male patients. There were 20 women and 130 men. Five patients were Negroes, two were Mexican and the remainder were of North European extraction. The immediate mortality rate during the first four weeks of illness in the series was 35.3 per cent. This is higher than the rate in some other reported series and this relatively high mortality rate is probably to be attributed to the inclusion of several cases with previous infarctions and of several complicated by other serious diseases, as well as to the rigid criteria of case selection which tended to exclude milder cases.

## RESULTS

The results of the study will be reported under certain clinical features of special interest.

*Relationship of Duration of Pain to Mortality Rate.* Duration of pain lends itself to quantitation somewhat better than intensity or quality of pain. It is recognized, however, that error arises in several possible ways: Sometimes it is difficult to ascertain which one of a long series of pains signalizes the infarction; the use of analgesics shortens the pain by unknown periods of time; severe pain is often followed by vague discomfort which makes the time of cessation uncertain. In spite of these facts it was possible to correlate the duration of pain with other significant features of the disease.

It should be emphasized that patients who succumbed to episodes of possible acute myocardial infarction before reaching the hospital were not included in this study.

* From the Department of Internal Medicine, Southwestern Medical College, Dallas, Tex.

Many patients die after only a few moments of pain; and since in many of these cases adequate historical data are often not obtained, the exact diagnosis may remain in doubt unless a postmortem examination is performed. While the exclusion of this type of case undoubtedly would reduce the mortality rate for the group of patients with pain of short duration, no data were available on such cases which are often seen by the coroner. Hence, all conclusions in the present study pertain only to patients with acute myocardial infarction who survived to reach the hospital, and the deaths recorded occurred during their period of hospitalization for the acute illness. Deaths occurring after a period of four weeks were not considered as being caused by the attack of acute myocardial infarction.

In this series patients with pain of less than five hours' duration usually survived the attack. (Fig. 1.) Only one out of nine of this group succumbed. As the duration of pain increased an increasing proportion of the cases terminated fatally. The proportion of deaths which occurred increased from 11.1 per cent in the group lasting less than five hours to 34.3 per cent in the group lasting five to twenty-five hours, and was highest (38.7 per cent) among those patients with the longest duration of pain (25 to 120 hours). Because of the possibility of error in determining the exact period of persistence of pain in the cases in which pain of long duration (72 to 120 hours) was reported, the data were re-evaluated excluding these cases. No change in the general tendency for the mortality rate to rise, with increasing duration of pain, was noted in the remaining cases.

For purposes of studying the significance of pain location, the cases were grouped, as will be discussed later, according to the various areas in which pain was felt. In the series of cases with anterior trunk pain alone it was noted that both duration of pain and mortality rate had their highest figures. When the relationship between duration of pain and immediate mortality rate was studied in the subgroups separated according to location of pain, the same results were noted, i.e., the number of patients who succumbed during the acute phase of the illness increased when the duration of perceptible pain was longest. To ascertain the possible influence of the multiple infarct cases on the relationship of duration and mortality, the data were also re-evaluated excluding these cases. No significant changes were noted when first attacks of myocardial infarction alone were considered, the mortality rate rising with increasing duration of pain.

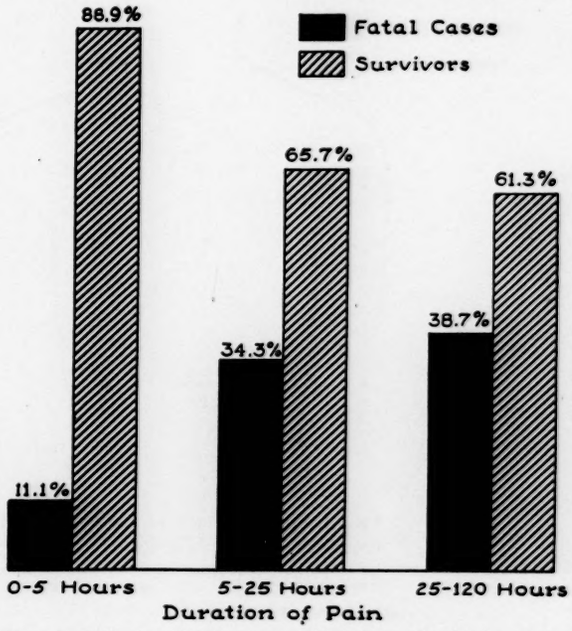



FIG. 1. Relationship between duration of pain in acute myocardial infarction and mortality rate.

TABLE I
SITE OF PAIN

| | Per Cent* |
|---|---|
| Anterior trunk | 100 |
| Substernal and/or precordial | 93 |
| Substernal | 82 |
| Left upper extremity | 64 |
| Right upper extremity | 33 |
| Anterior trunk alone | 29 |
| Precordial | 24 |
| Trunk, neck and both upper extremities | 11 |
| Posterior thorax | 9 |
| Epigastric | 7 |
| Epigastric alone | 2 |
| Jaw | 2 |
| Trunk and right upper extremity alone | 2 |
| Trunk and neck only | 1.3 |
| Epigastric and both upper extremities | 0.6 |

* These percentages are based on 139 cases with history of pain.

*Location of Pain.* There was anterior trunk pain in all the cases with a definite history of pain. In most instances it was described as substernal. In three cases pain was limited to the epigastric region. In one case the pain was in the epigastrium and both arms. In nineteen cases the anterior trunk pain was described as precordial. In some it was both precordial and substernal in location. In no case of the series was there absence of anterior trunk pain, as was noted in one instance by Levine and Rosenbaum.[4] In their case isolated left arm pain occurred with myocardial infarction. Location and radiation of pain are grouped together in considering the sites of pain. Table 1 reveals the frequency of occurrence of pain at various sites.

No significant relationship between the location of the infarct and the site in which pain was perceived was noted in this series. Posterior and anterior infarcts seemed to differ only slightly in the various regions to which pain radiated. There seemed to be a slight tendency for posterior infarctions to exhibit a higher incidence of neck and upper abdominal pain and for anterior infarcts to exhibit a higher incidence of anterior and posterior chest pain and arm pain. These differences were very slight and were probably not significant.

There was no correlation between size of infarct and the extent of the pain radiation.

Patients with pain confined to the anterior trunk had a significantly greater mortality rate (59 per cent) than those with pain radiation beyond the anterior trunk (18 per cent). If the cases are separated somewhat differently, a similar finding is noted; patients having no more extensive radiation than trunk and left arm had a mortality rate of 43 per cent whereas those with wider radiations than this had a 16 per cent mortality. The two large divisions of the series as to site of pain are depicted in Figures 2 and 3 along with corresponding pain duration and mortality rate. Increasing mortality, increasing pain duration and confinement of pain site to the trunk are apparently related and likewise the reverse relationship holds.

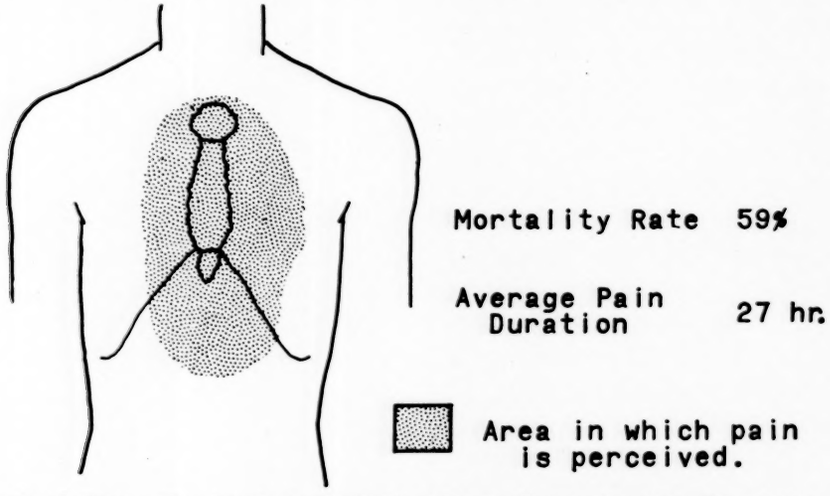



FIG. 2. Pain confined to the trunk. In forty-four patients pain was confined to the trunk alone. In this group the mortality (59 per cent) was higher than in patients in whom the pain radiated elsewhere. (Compare with Figure 3.)

*Pain Patterns.* A strict classification of the diverse clinical forms of myocardial infarction is quite difficult. However, we found that in regard to time relationships of episodes of pain and duration of pain, all of the patients from whom adequate histories had been obtained fell into certain fairly well defined groups which are listed below. The histories of twelve patients were inadequate so far as data regarding the

onset of pain and preceding angina or premonitory pain were concerned.

*Painless Infarctions.* Eleven patients gave no history of pain. That these were extremely grave and complicated cases is shown by the fact that all eleven failed to survive the infarction. Autopsies were performed on nine. The causes for the failure to obtain a history of pain were obvious in eight of these cases: five of this group were in coma, one was psychotic and one was in diabetic acidosis and semi-stuporous. Still another died shortly after operation before he had recovered from the anesthesia. Two patients presented primarily symptoms of congestive failure which had been of sudden onset and gave no history of pain although they were questioned specifically on this point. Following prostatic resection, another patient died suddenly on the tenth postoperative day from rupture of an infarcted area in the left ventricle. It is probable that pre- and postoperative medications masked the pain in this case although other factors may also have been involved.

*Intermittent Pains without Severe Prolonged Pain.* While the usual picture in myocardial infarction is that of a bout of extended severe pain, ten of our patients had a series of only relatively mild pains so that it was impossible to indicate any one pain as that occurring with the onset of infarction. Five of these patients had one- to three-hour episodes over a period of four to six days. Four others had frequent attacks lasting five to fifteen minutes, which were similar in one case to the angina which the patient had been having for fourteen months, except that they occurred at rest. A brief summary of the ninth case is given.

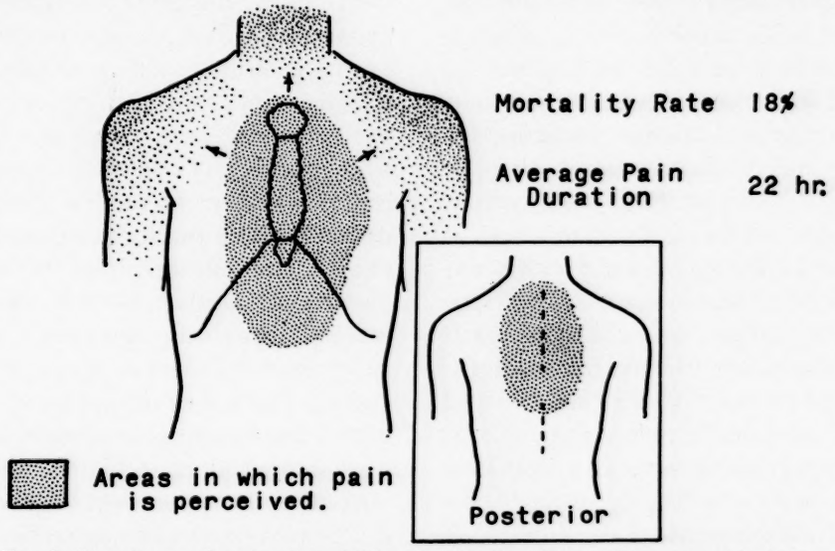



FIG. 3. Anterior trunk pain plus additional radiation. Ninety-five patients had pain also felt in areas outside the trunk. In this group the mortality (18 per cent) was less than in the groups confined to the thorax. (Compare with Figure 2.)

CASE NO. 70. A thirty-one year old white male, who had arterial hypertension and a severe anxiety reaction, began having substernal pain of a mild burning character about one week before admission to the hospital. The pains lasted five to forty minutes at a time, sometimes radiated to both arms and were said by the patient to be unrelated to exertion. However, in the hospital it was demonstrated that the pain could be reproduced by exertion and relieved by rest and nitroglycerin. Electrocardiograms before and after exercise were normal. The pains recurred at frequent intervals for forty-five days without significant change in severity or duration and then stopped suddenly, following which a large Q wave in Lead $V_4$ in the electrocardiogram developed concomitant with an elevated sedimentation rate. When last seen the patient was still free of pain.

In spite of the apparent mildness of the pain, two of this group died, a mortality

of 20 per cent. The average age was forty-nine years.

*Sudden Onset of Pain without Preceding Angina or Premonitory Pain.* We were able to find only twenty-eight cases in which there was no history of any type of chest pain experienced before the onset of the pain associated with the infarction. Except for four patients who had had previous infarctions not followed by angina pectoris, these individuals had been unaware of heart disease and had been engaging in ordinary activity. Four of these patients had the onset of pain while performing moderately hard work. It might have been expected that these individuals would be younger than the group as a whole but such was not the case since the average age for the twenty-eight patients was 57.7 years and this group contained only one of the patients under thirty-five years of age. The mortality rate was 21.4 per cent. Of the twenty-five cases in which the location of the infarction could be determined, nineteen were found to be anterior and only six posterior.

*Premonitory Pain Soon Followed by Prolonged Infarct Pain.* There were twenty-four cases in this group, eight of whom died during the attack, a mortality rate of 33.3 per cent. The average age was 47.7 years and the duration of infarct pain averaged 19.3 hours. None of these patients had pain which would ordinarily be considered angina pectoris, as the pains were not brought on by exertion, lasted longer than thirty minutes, and were not relieved by rest or by nitroglycerin when this drug was used. The duration of the episodes of pain preceding the infarction ranged from thirty minutes to three hours and antedated the infarction from one to thirty days. A few had only one episode of premonitory pain but the majority had two or more such episodes. In the few cases which were observed during the premonitory pain, laboratory evidences of tissue destruction did not occur and there was no temperature elevation. Obviously, it is impossible to state positively that some of the cases not observed during this period of premonitory pain had not had small infarctions. However, the pain seemed to correspond to that which has been described variously as status anginosus, acute coronary insufficiency or coronary failure and, when preceding an infarction, as preliminary pain.

*Preceding Angina Pectoris, with or without Premonitory Pain.* This was the largest group with sixty-five patients. The average age was 56.9 years, the mortality rate 29.2 per cent and the average duration of infarction pain 17.7 hours. Thirty-one of the infarctions were anterior, twenty-five were posterior and the location of the remainder could not be determined definitely from the electrocardiogram. The duration of angina ranged from one month to ten years and many had episodes of premonitory pain preceding the infarction, although a few had noted no increase in frequency or severity of the angina pectoris. A point of interest was the finding that the patients who developed posterior infarctions had had a somewhat longer average duration of angina pectoris. Of the twenty-one patients with anterior and the nineteen patients with posterior infarctions from whom a definite history as to the duration of angina was obtained, the anterior group had had angina pectoris for thirty-one months as compared to forty-eight months for the posterior group. This difference, if it be significant, cannot be related to the differences in age, as the average age was practically the same for the patients with anterior and posterior lesions with preceding angina.

## COMMENT

The data presented in this study indicate a relationship between the duration of pain in acute myocardial infarction and the immediate mortality rate. While the exclusion of patients who succumbed almost immediately to the disease might increase the mortality rate considerably in the group of cases with pain of less than five hours' duration, no data on such patients in whom the diagnosis was proven were available. The evidence obtained from the patients

who survived to reach the hospital suggests that the hazard of death increased when the pain of the acute attack lasted longer. It should be pointed out, however, as shown in Figure 1, that this is a general trend and that pain of short duration does not necessarily indicate a favorable prognosis; since several patients, who had pain of less than five hours' duration, succumbed to the disease while in the hospital. As a group, however, the chances for survival appeared best in these cases with pain of short duration. By contrast, it should be pointed out that pain of quite long duration, during an episode of acute myocardial infarction, does not necessarily indicate a fatal prognosis, since several patients survived such a period of relatively prolonged pain. In general, however, the chances for a fatal outcome appeared greater with such prolonged pain. In this regard, then, the presence of persistent pain appeared to be an unfavorable and undesirable symptom.

In what manner can the persistence of pain affect the outcome in the acute attack or during convalescence therefrom? The answer to this question seems intertwined with the mechanism of causation of pain in coronary artery disease. Although the theory of increased intravascular tension has had its adherents since the time of Allbutt,[6] the prevailing view that appears best to explain the causation of pain is that of Keefer and Resnick[7] who believed such pain was caused by myocardial anoxia. This theory has been supported by the observations of Lewis,[8] of Herrick[9] and of Katz[10] and appears to be in accord with a large body of clinical and laboratory evidence. The immediate cause of death in patients with recent severe impairment of coronary flow is most frequently an acute disturbance of cardiac rhythm, often with ventricular tachycardia or fibrillation as the immediate precursor of cardiac arrest. Anoxia or ischemia of the myocardium (irrespective of whether it exerts a direct or a reflex harmful effect) produces a very hazardous state, with sudden death as a constant potential danger. Since this dangerous state of myocardial irritability is signaled by a sensation of discomfort, pain is a warning signal of great moment. Its continued presence, when viewed in the light of these concepts, indicates the continuation of a dangerous state of myocardial dysfunction. The longer that pain persists, therefore, the greater the hazard to the patient's life. This is attested to by the increasing mortality rate when pain lasts for longer periods of time. It should be recognized that in a minority of cases death during the first four weeks following an acute myocardial infarction is caused by thromboembolic complications or by rupture of the heart. In cases in which death is due to such causes the duration of pain might well bear no relation to the mortality rate. In general, however, insofar as prolonged pain was an index of coronary insufficiency, it appeared to be a serious omen.

When the significance of pain confined to the chest is considered, it would appear, from the present study, that there is a somewhat higher mortality among the group of patients in which pain did not radiate into the extremities or neck. This has previously been noted by Levine and Rosenbaum[4] in the case of anterior myocardial infarcts. The significance of this finding is difficult to understand. It is possible that patients who have severe infarction, to which they succumb, may have a greater degree of shock develop soon after the onset of the myocardial infarction. If this is so, it is well known that the development of shock dims the sensorium and may thus, in this fashion, decrease the overflow phenomena of impulses, which are apparently a part of the picture of referred pain. However, it must be admitted that this explanation is entirely theoretical and that no good cause is known for this phenomenon.

When the types of onset of myocardial infarction are considered, it becomes apparent that they form a gradation of increasing severity, represented by the following sequence: (1) Painless infarction; (2) intermittent pains without severe prolonged

pain; (3) sudden onset of myocardial infarction without any preceding pain; (4) premonitory pain of short duration followed by prolonged infarct pain and (5) preceding angina pectoris of some duration, with or without premonitory pain. From the work of Schlesinger and Blumgart[11] it is known that patients who have severe angina pectoris have had rather extensive pre-existing coronary artery disease. It is entirely probable that the type of onset is related, in a rough degree, to the amount and severity of pre-existing coronary artery damage.

Thus patients who have no pain or very slight pain may have a relatively slight degree of coronary artery damage, or may have only one or more major branches of the coronary artery tree involved. It is also possible, however, that previous ischemia has caused degeneration of sensory autonomic nerve fibers, with consequent diminution of absence of the ability to carry pain impulses. In the case of patients with intermittent pains without severe prolonged pain, it is probable that the activity of the patient, to a considerable extent, influences the development of the myocardial infarction. Such patients may often continue to be physically active with a markedly diminished coronary flow and thus accelerate the rate at which muscle dies. The same is also probably true of patients who have premonitory pain, since many of these patients develop their pain during a period of physical activity, and this activity, as in the preceding group, may have been responsible in part for development of the infarction. It should also be borne in mind, however, that in many cases the premonitory pain may actually be symptomatic of a marked discrepancy between the need for and the supply of blood, which persists over a period of hours or days. In patients who have a sudden onset of pain without preceding angina or premonitory pain, the most likely hypothesis is that these patients have had a relatively rapidly forming thrombus develop, or that they have had a subintimal hemorrhage with a fairly rapid occlusion of a major branch of the coronary artery tree. Finally, in the patients with long-continued angina preceding the infarction there is evidence that these patients have had severe interference with coronary flow and that the infarction is only one in a series of multiple events related to this pre-existing coronary artery disease.

## SUMMARY

1. The duration, location, radiation and mode of onset of pain have been studied in 150 cases of proven acute myocardial infarction.

2. There appeared to be a definite relationship between the duration of pain and the mortality rate, the latter rising as the pain persisted over longer periods. There were, however, many patients with pain of short duration that succumbed to the disease, and there were also cases of pain of long duration in patients who survived. As a group, however, patients with the longest duration of pain had the highest mortality rate.

3. When location of pain was considered, it was noted that pains confined to the thorax without radiation definitely had a higher mortality rate than pains which radiated to the extremities and neck. The reasons for this are not clear but may be related to shock.

4. The mode of onset of pain in acute myocardial infarction is extremely variable. It may be painless; it may consist of a few short pains of intermittent type which are not severe; it may appear suddenly without any premonitory pain; it may appear following premonitory pain of long duration or it may appear after a long preceding period of angina. The recognition of these fundamental modes of onset is of importance in establishing an early diagnosis.

## REFERENCES

1. Heberden, William. Some account of a disorder of the breast. *M. Tr. Roy. Coll. Physicians, London*, 2: 52, 1772.
2. Willius, F. A. Life expectancy in coronary thrombosis. *J. A. M. A.*, 106: 1890, 1936.
3. Mintz, S. S. and Katz, L. N. Recent myocardial infarction. *Arch. Int. Med.*, 80: 205, 1947.

4. Rosenbaum, F. F. and Levine, S. Prognostic value of various clinical and electrocardiographic features of acute myocardial infarction. *Arch. Int. Med.*, 68: 913, 1941.
5. Wood, F. C., Bellet, S., McMillan, T. M. and Wolferth, C. C. Electrocardiographic study of coronary occlusion. *Arch. Int. Med.*, 52: 752, 1933.
6. Allbutt, C. Diseases of the Arteries Including Angina Pectoris. Vol. 2. London, 1915. MacMillan & Company.
7. Keefer, C. S. and Resnick, W. H. Angina pectoris, a syndrome caused by anoxemia of the myocardium. *Arch. Int. Med.*, 41: 769, 1928.
8. Lewis, Thomas. Pain in muscular ischemia. *Arch. Int. Med.*, 49: 713, 1932.
9. Herrick, J. B. Clinical features of sudden obstruction of the coronary arteries. *J. A. M. A.*, 59: 2015, 1912.
10. Katz, L. N. Mechanism of pain production in angina pectoris. *Am. Heart J.*, 10: 322, 1935.
11. Blumgart, H. L., Schlesinger, M. J. and Davis, D. Studies on the relation of the clinical manifestations of angina pectoris, coronary thrombosis and myocardial infarction to the pathologic findings with particular reference to the significance of the collateral circulation. *Am. Heart J.*, 19: 1, 1940.

# Congestive Heart Failure of Renal Origin*

## *Pathogenesis and Treatment in Four Cases of Carbon Tetrachloride Nephrosis*

CHARLES K. FRIEDBERG, M.D.
*New York, New York*

RECENT interest has been focused on a clinical-pathologic syndrome of varied etiology characterized by severe oliguria and uremia and classified under the heading of lower nephron nephrosis.[1] Numerous reports of this condition in the past few years have been concerned predominantly with the pathogenesis and pathologic physiology of the renal disturbance[2–7] or with therapeutic technics to clear the blood of retained waste products until the damaged kidney undergoes spontaneous repair.[8–12] Recent studies[13,14] have emphasized that urinary suppression and renal insufficiency of lower nephron nephrosis are self-limited disturbances and that the therapeutic value of such technics as the artificial kidney, peritoneal lavage, intestinal dialysis or exsanguination transfusion is therefore difficult to assess.

This presentation of four cases of lower nephron nephrosis due to the inhalation of carbon tetrachloride is limited to a discussion of the occurrence, pathogenesis, prevention and treatment of associated congestive heart failure. It is designed primarily to emphasize that the deficient excretion of sodium and water due to primary renal disease can produce the complete syndrome of congestive heart failure without cardiac disease. In ordinary cases of heart failure the kidney may be regarded as the effector organ whose dysfunction is in part responsible for the clinical phenomena, but cardiac disease is the primary causative abnormality. In the cases of lower nephron nephrosis which are herein reported the clinical features of heart failure appeared in young and hitherto healthy individuals without past or present cardiac disease and could be attributed to the primary renal disease.

Secondarily these cases are presented not only to re-emphasize the danger of fatal pulmonary edema due to overzealous administration of massive quantities of fluids but to stress the frequency of congestive heart failure with intakes of sodium and water which are not ordinarily excessive for individuals with normal hearts. The danger of fatal pulmonary edema due to massive intravenous infusions and the futility of such measures to overcome urinary suppression and progressive azotemia have become generally recognized. But there is still inadequate recognition of the frequency of edema and other evidences of congestive heart failure induced by the administration of *moderate* amounts of fluid which have no egress because of the complete or almost complete cessation of renal excretion of sodium and fluid.

Finally this report is designed not merely to reiterate the self-limited nature of toxic nephrosis and the merits of conservative therapy but more particularly to stress that the treatment of carbon tetrachloride nephrosis should be directed chiefly toward the prevention and control of heart failure without regard to the concomitant azotemia and almost always without regard to the associated acidosis or electrolyte disturbances. Emphasis on the prevention and treatment of congestive heart failure is justified by the observation that fatalities

* From The Mount Sinai Hospital, New York, N. Y.

from lower nephron nephrosis are most commonly due to this complication, and by the fact that the renal disturbance itself is of relatively brief duration with spontaneous diuresis and recovery usually beginning within two weeks of the time of exposure to the chemical. In the absence of iatrogenic disturbances, azotemia, hypochloremia and acidosis during this brief period are rarely if ever of sufficient degree or duration to cause death.

This emphasis may seem superfluous in view of the admonitions of Kugel,[15] Burnett,[16] Muirhead and Fromm[17] and Strauss,[18] among others, that the fluid intake should be restricted because of the danger of overhydration and consequent pulmonary and generalized edema. Despite these warnings, however, my experience has been that most patients with lower nephron nephrosis and more particularly those with carbon tetrachloride nephrosis already present some evidence of "overhydration" or congestive heart failure when first seen in the hospital. This is due partly to misinterpretation of "excessive fluid intake" to mean massive fluid intake and partly to compromises with fluid and sodium restriction which are provoked by a desire to neutralize acidosis, correct hyponatremia and hypochloremia and maintain an adequate caloric intake.

Those writers who have most strongly emphasized the need for restricting fluids contribute to this dilemma by their other therapeutic recommendations. Kugel[15] advocated a basic daily intake of 700 cc. of physiologic saline solution (6.3 gm. of sodium chloride). Strauss[18] recommended that 1 L. of one-sixth molar sodium lactate solution be given in the presence of acidosis, that physiologic saline be given intravenously sufficient to replace the sodium chloride lost in the vomitus and that, if the plasma sodium is low even in the presence of edema, the patient may be benefited by an intravenous solution of 3 to 5 per cent sodium chloride with or without sodium bicarbonate. Since acidosis, vomiting and hyponatremia are frequent if not the rule in these cases, there is great pressure to administer sodium, which seems theoretically justified but which nevertheless induces edema or other manifestations of heart failure, contrary to theoretic calculations. Thus although Kugel[15] particularly stressed the importance of fluid restriction, the ineffectiveness of his treatment is suggested by the inability to prevent or control congestive heart failure in both of his reported cases of toxic nephrosis. In his first case due to carbon tetrachloride inhalation "frank congestive failure" first developed after he had altered previous therapy so as to discontinue all intravenous fluids and allow only a "minimum" of oral fluid. This minimum consisted of 800 cc. and 900 cc., respectively, on the two days preceding the appearance of overt heart failure. The onset of spontaneous diuresis the following day accounted for recovery. Similarly, in his second case of nephrosis due to transfusion reaction severe congestive heart failure developed and progressed between the third and seventh day of the illness despite a fluid intake of only 650 to 1,350 cc. on those days. In one of Strauss's cases of lower nephron nephrosis[18] death occurred six hours after an intravenous infusion of 1,000 cc. of physiologic saline and 500 cc. of one-sixth molar sodium lactate solution although no fluids had been given during the previous twenty-four hours.

These and other observations suggest that the advised restriction of fluids has been quantitatively inadequate or that insufficient stress has been placed on the necessary degree of sodium restriction. The importance of the quantitative degree of sodium restriction in the management of carbon tetrachloride nephrosis is analogous to that in the treatment of conventional congestive heart failure. Physicians, long aware of the importance of sodium restriction, often failed to control heart failure because their restriction of sodium chloride intake to 2 to 5 gm. daily permitted an excessive sodium intake. In cases of lower nephron nephrosis, in which there may be no excretion of sodium at all, the seemingly moderate

quantities of sodium allowed or recommended to correct acidosis or electrolyte balance are excessive and may foster the clinical phenomena of heart failure despite the restriction of fluid intake.

I have pointed out that the recommendation for sodium and fluid restriction in lower nephron nephrosis is in need of more exact quantitative interpretation. But it should also be mentioned that the basic concept of sodium and fluid restriction in this condition is not universally accepted. Thus Hoffman and Marshall[19] recently recommended the "careful" induction of edema by intravenous administration of fluids in an effort to dilute the retained toxic substances—the reverse of sodium and fluid restriction. Edema or congestive heart failure appeared in all six of their patients but only one died.

While there are many common features and common problems in all forms of lower nephron nephrosis regardless of etiology, this report is concerned essentially with the cases due to carbon tetrachloride poisoning. The probability exists that pathologic changes and their sites of localization are not absolutely identical in all etiologic types of lower nephron nephrosis and that the specific tubular functions which are spared or damaged and the degree of damage are not exactly the same. Modifications in treatment, corresponding to these variations in renal disturbance in the different groups of lower nephron nephrosis, may be indicated. Variations in response and treatment may depend also on the occurrence and persistence of hemorrhage, shock or other disturbances associated with the primary disease responsible for the lower nephron nephrosis.

Special circumstances associated with the "heart failure" of lower nephron nephrosis demand important quantitative and qualitative modifications from any "routine" treatment ordinarily utilized in the management of congestive heart failure secondary to cardiac disease. The treatment will be noted after a brief presentation of the case reports. It appears proper to emphasize that this subject is of special concern to the general physician who first sees these cases because it is the management in the first week of the disease which usually determines the outcome.

## CASE REPORTS

CASE 1. A twenty-six year old male oxygen welder was admitted because of anuria, dyspnea and orthopnea. The onset of his present illness, characterized by nausea, vomiting and epigastric burning, had followed very recent exposure to vats containing sulfuric acid and carbon tetrachloride. In the first five days of his illness he was in another hospital where only a few cc. of bloody urine were obtained by catheterization on the day of admission. There was percussion dullness over both lower lobes of the lungs. There were hemorrhages in the sclerae and the sputum was blood-tinged. The non-protein nitrogen of the blood was 112.5 mg. per 100 cc. Despite the administration of 10 L. of fluid, chiefly by vein, in a period of forty-eight hours the total urinary output was only 40 cc. Blood pressure was 156 systolic and 86 diastolic. The cervical veins appeared distended. The blood chloride concentration was 480 mg. per 100 cc. and the carbon dioxide combining power 38 volumes per cent. Due to continued anuria the patient was referred to The Mount Sinai Hospital for possible treatment with the artificial kidney.

Examination disclosed a very dyspneic and orthopneic man who was coughing up bloody sputum. There was mild cyanosis of the lips and nailbeds. A small subconjunctival hemorrhage was noted. There were signs of congestion and fluid at the bases of the lungs. A blowing systolic murmur was audible over the cardiac apex. The liver was enlarged to two finger-breadths below the costal margin. The blood pressure was 170 systolic and 90 diastolic. The venous pressure was 10.5 cm. and rose on right upper quadrant pressure. The circulation time (calcium gluconate) was 11 seconds. The electrocardiogram showed no abnormality. X-ray examination of the chest disclosed infiltrations resembling pulmonary edema and bronchopneumonia.

Laboratory data were as follows: Urine: grossly bloody; specific gravity 1.020; albumin 2 plus. Blood: hemoglobin 83 per cent; erythrocytes 4,400,000; leukocytes 12,400; polymorpho-

nuclear cells, segmented 85 per cent, non-segmented 9 per cent; lymphocytes 2 per cent; monocytes 4 per cent. Blood urea nitrogen 97 mg. per 100 cc.; creatinine 14.7 mg. per cent; non-protein nitrogen 109 mg. per cent; carbon dioxide combining power 40 volumes per cent.

The history of carbon tetrachloride exposure was not elicited at the time of admission and the oliguria and azotemia were attributed to acute glomerulonephritis. There was, however, considerable disagreement as to the nature of the renal and pulmonary abnormalities and as to the existence or character of the heart failure.

The patient was placed in an oxygen tent and tourniquets applied to the extremities. It was believed that digitalis was not indicated. Fluids were limited but their intake reached 920 cc. in twenty-four hours, during which the output was only 190 cc. Four hundred cc. were given in the form of intravenous fluids containing sodium. Dyspnea, orthopnea and restlessness persisted and cyanosis became prominent whenever the patient was taken out of the tent. On the day after admission the pulse was 120 per minute, respiratory rate 40 to 60 per minute and blood pressure rose to 200 systolic and 130 diastolic. The patient became very restless and apprehensive and suffered a convulsion which was followed by gasping irregular respiration, bloody froth at the mouth and death within fifteen minutes.

Postmortem examination revealed pulmonary edema; bilateral hydrothorax; ascites; nutmeg liver with central and mid-zonal necrosis; heart weighing 370 gm. but apparently normal; diffuse toxic nephrosis with severe degeneration of the renal tubules and relatively normal glomeruli.

*Comment.* This man was suffering from advanced pulmonary edema at the time of admission, undoubtedly due to the huge amounts of fluids administered parenterally, 10 L. having been given in a two-day period during which the damaged kidneys had excreted less than 100 cc. The risk of further overloading the circulation was recognized but apparently not completely understood. For although fluids were limited, they were not sufficiently restricted and small intravenous infusions containing sodium were given to combat acidosis. Thus the exaggerated risk of acidosis led to an unwise compromise with the much more dangerous and imminent risk of congestive heart failure. Furthermore, the seriousness of the pulmonary edema was underestimated in treatment and death occurred before urgent phlebotomy could be performed.

Case II. Eight days before admission a thirty year old mechanic was exposed to carbon tetrachloride fumes for five hours while cleaning a machine in a small unventilated room. This was followed by generalized aches, especially low back pain, weakness, nosebleeds, black and blue spots, vomiting of blood and tarry stools. Hematuria occurred on the second day after exposure to the carbon tetrachloride and this was associated with severe oliguria or anuria. On the third day the patient was hospitalized in another institution where he received fluids intravenously because of intense vomiting, oliguria and a blood urea nitrogen which rose from 62 to 95 mg. per 100 cc. The fluids included 7,500 cc. of saline given intravenously in five days as well as 1,600 cc. per os and 700 cc. per rectum during the same period. On the day before admission to The Mount Sinai Hospital the patient was phlebotomized because of pulmonary edema. The patient had been a heavy drinker and had taken ten highballs daily for many years.

Examination revealed an acutely ill man, with uremic odor to his breath, puffy face, subconjunctival hemorrhage and periorbital ecchymoses. There was a short systolic murmur over the precordium. The second pulmonic sound was accentuated. There was percussion dullness over the right lower lobe where rhonchi could be heard. The blood pressure was 160 systolic and 100 diastolic. The venous pressure was 19 cm. with a rise on right upper quadrant pressure to 22 cm. The circulation time (calcium gluconate was 8 seconds. The electrocardiogram showed no significant abnormality.

Laboratory data were as follows: Urine: acid, specific gravity 1.010 to 1.016; albumin 2 plus; many erythrocytes; occasional leukocytes. Blood: hemoglobin 10.5 gm.; erythrocytes 3,410,000; platelets 170,000; leukocytes 10,450 with polymorphonuclear segmented cells 71 per cent, non-segmented 2 per cent, eosinophiles 5 per cent; lymphocytes 10 per cent; monocytes 6 per cent; hematocrit 39 per cent; blood urea nitrogen 108 mg. per 100 cc., non-protein nitrogen

170; chlorides 423 mg. per 100 cc.; carbon dioxide 41 volumes per cent.

The patient passed very scanty amounts of dark brown urine containing blood. On the day after admission he was treated with the artificial kidney for five hours. The blood urea nitrogen fell from 108 mg. to 55 mg. per 100 cc. Because of epistaxis and other hemorrhagic phenomena the patient was given a transfusion. Five days later he was again treated with the artificial kidney because of a moderate rise in urea nitrogen, persistent oliguria and vomiting. He suffered severe gastrointestinal bleeding and shock. The hemoglobin fell to 5 gm., the hematocrit to 19.5 and the total circulating blood volume was 18 per cent below normal although the plasma volume was increased by 20 per cent.

The patient's fluid intake varied between 875 and 2,200 cc. daily during the oliguric period. Except when he was given a transfusion the fluids did not contain sodium. The fluid intake was neutralized by relatively severe bleeding as well as by persistent vomiting which varied usually between 500 and 1,500 cc. daily. A pronounced diuresis started on the seventeenth or eighteenth day of the illness. In the subsequent twelve-day period the patient lost more than 20 pounds, due almost exclusively to loss of fluid. The blood urea nitrogen diminished gradually and became normal on the thirty-fifth day of the illness.

*Comment.* Excessive administration of fluids during the first week of illness led to acute pulmonary edema which required a phlebotomy for relief. However, the intake was not enormous, averaging 1,900 cc. per day for five days. Thereafter fluids, and especially fluids containing sodium salts, were relatively limited although more were given than is usually desirable. That heart failure did not recur may be attributed to two factors, severe bleeding and persistent excessive vomiting which tended to result in a static or slightly negative fluid balance. There was no hypervolemia.

CASE III. A forty-nine year old male laboratory worker was admitted nine days after exposure to carbon tetrachloride fumes. In addition to nausea, recurrent vomiting of bloody material and tarry stools, severe oliguria had been present for six days. At another institution he had been given 5,000 cc. of fluid intravenously in forty-eight hours and this had been followed by bleeding, blurring of vision and puffiness of the face. The record showed that he had been passing only one or two ounces of urine daily.

Examination revealed fine moist rales at the bases of the lungs and signs of fluid in both pleural cavities. There was a faint systolic murmur and presystolic gallop rhythm over the cardiac apex. The second pulmonic sound was accentuated and louder than the second aortic sound. The liver was enlarged two fingerbreadths below the costal margin and there were signs of fluid in the peritoneal cavity. There was periorbital and presacral edema. The blood pressure was 184 systolic and 116 diastolic. The venous pressure was 11.5 cm. and the circulation time 11.8 seconds.

Laboratory data were as follows: Urine: specific gravity 1.010; Ph 6.0; albumin 3 plus; occasional erythrocytes, leukocytes and granular casts; hemoglobin 8.4 gm.; erythrocytes 2,880,000; blood urea nitrogen 78 mg. per cent, chlorides 507 mg. per 100 cc.; carbon dioxide combining power 35 volumes per cent.

Because of the evidences of congestive heart failure the intake was limited to 500 cc. daily of sodium-free fluid consisting essentially of fruit juice. However, due to the diminution in plasma chlorides and bicarbonate and a low calculated plasma sodium (104 mEq.), 1,000 cc. of 5 per cent glucose in saline was administered intravenously and on the second day after admission 10 gm. of sodium chloride were given orally. These measures appeared justified also by the fact that the patient was beginning to secrete increasing quantities of urine. However, on the following day the patient's respirations were shallow, rapid and labored; he became restless and dyspneic and by evening there were frank signs of pulmonary edema. The circulation time was 13 seconds. The cervical veins were distended and the venous pressure was 15.5 cm. with a rise to 18 cm. on right upper quadrant pressure. Fortunately, the patient was in the thirteenth or fourteenth day of his illness and spontaneous diuresis had already begun. Thereafter the urinary output was very large and the patient lost 18 pounds in the next three days and a total of 35 pounds in seventeen days. The blood urea nitrogen concentration continued to mount to 131 mg. on the eighteenth day and thereafter diminished until it reached normal

on the thirty-second day after exposure to the carbon tetrachloride.

*Comment.* The patient presented evidence of anasarca which was attributed in part to the excessive intravenous administration of fluids prior to admission. The fear of hypochloremia and acidosis led to the administration of sodium chloride and the precipitation of acute pulmonary edema. A normal to rapid circulation time misled some observers into overlooking the presence of pulmonary congestion.

CASE IV. Ten days before admission a thirty-eight year old man, who had been drinking heavily of beer and whiskey, was exposed for four hours to carbon tetrachloride which he was using to clean a washing machine in a poorly ventilated cellar of his home. Two days later he developed oliguria for which he was hospitalized at another institution where he received 4,500 cc. of fluids intravenously. On the second day of this regimen he became dyspneic and on the third day suffered an attack of acute pulmonary edema.

Examination on admission to The Mount Sinai Hospital revealed a very dyspneic, orthopneic man who was coughing up frothy pink sputum. His cervical veins were distended. The lungs were filled with coarse bubbling rales. The heart was somewhat enlarged and a systolic murmur and gallop rhythm were audible at the apex. The liver was enlarged three to four fingerbreadths below the costal margin and was tender. Blood pressure was 190 systolic and 110 diastolic.

Laboratory data were as follows: Urine: specific gravity 1.008; albumin 2 plus; moderate number of leukocytes and erythrocytes. Blood: hemoglobin 13.9 gm.; leukocytes 14,800 with 82 per cent segmented and 1 per cent non-segmented polymorphonuclear cells; lymphocytes 1 per cent; monocytes 4 per cent; myelocytes 1 per cent. Stool: guaiac test for occult blood (4 plus). Blood urea nitrogen 117 mg. per cent; chlorides 470 mg. per cent and carbon dioxide 31 volumes per 100 cc.

Two phlebotomies of 600 cc. each had to be performed to control the pulmonary edema. Morphine, oxygen by positive pressure, rapid digitalization and the application of tourniquets had not been sufficiently effective. The heart failure was controlled by the following day and spontaneous diuresis began four days after admission and the thirteenth day after exposure to carbon tetrachloride. Until the fifteenth day his intake had been limited to 500 cc. of fluids without any sodium. His blood urea nitrogen reached its maximum of 226 mg. on the sixteenth day after exposure and fell thereafter, reaching normal on the twenty-seventh day.

*Comment.* The patient was admitted in severe pulmonary edema which had been induced by the intravenous administration of sodium-containing fluids during the first week of the oliguria. After this was controlled there was no further evidence of heart failure on a regimen which permitted no more than 500 cc. of fruit juice given orally. Although the urea nitrogen reached 226 mg. per cent, spontaneous diuresis occurred at its usual time and recovery of renal function ensued as early as in other cases in which larger amounts of fluid had been given or in which efforts had been made to clear the blood stream of waste products by artificial means.

## COMMENTS

*Manifestations of Heart Failure in Carbon Tetrachloride Nephrosis.* There is some question as to the applicability of the term congestive heart failure to cases in which there is no clinical, electrocardiographic or pathologic evidence of cardiac disease and no previous history suggesting cardiac damage. Nevertheless, at some stage in the clinical course most or all of the cardinal features of congestive heart failure were manifested in the reported cases: dyspnea, orthopnea, attacks of pulmonary edema, engorged veins and elevated venous pressure, hepatojugular reflux, enlargement of the liver, subcutaneous edema, hydrothorax, ascites and gallop rhythm. In the patients with pronounced pulmonary congestion the second pulmonic sound was accentuated and louder than the second aortic sound, despite the fact that there was distinct systemic hypertension. Furthermore, as in cases of congestive heart failure associated with the common cardiac dis-

eases, the symptoms were precipitated or intensified by sodium-containing fluids and alleviated by sodium and fluid restriction or, in acute episodes, by phlebotomy.

While cardiac failure may be defined physiologically in terms of the adequacy of the cardiac output, in practice it is defined as a clinical syndrome and recognized by the above mentioned clinical features.[20] From the latter viewpoint the criteria for "congestive heart failure" were fulfilled in these cases of carbon tetrachloride nephrosis even though there was no evidence of underlying cardiac disease and no evidence of a deficient cardiac output.

Of interest is the frequent observation in these and other cases of lower nephron nephrosis with heart failure that the circulation time is normal or diminished. This has often been responsible for failure to recognize the presence of congestive heart failure or even of impending pulmonary edema. The accelerated circulation speed may be due to the relatively pronounced anemia usually found in these cases. In some instances arterial anoxemia may be a contributory factor, for distinct cyanosis has been observed when the hemoglobin concentration was only 8 gm. per 100 cc. It is well known that the circulation time may be normal or diminished in cases of congestive heart failure if there is associated severe anemia or advanced pulmonary emphysema. Although the cardiac output was not actually determined, there is indirect evidence that these cases of carbon tetrachloride nephrosis fall in the group of high-output failure. Except in one instance following severe hemorrhage with a hematocrit below 20 the circulating blood volume was increased significantly beyond normal and the circulation speed was normal or rapid. This combination of enhanced blood volume and circulation speed denotes an augmented venous return and therefore an increased cardiac output.[20]

*Etiology and Pathogenesis.* In the usual type of congestive heart failure which follows chronic and progressive cardiac disease the initiating mechanism may be regarded as a deficient cardiac output while the clinical phenomena result from an impaired renal excretion of sodium and water. This impairment has been attributed to a reduction in renal blood flow, to diminished glomerular filtration, increased tubular reabsorption, increased renal venous pressure or other factors but the exact mechanism of the renal impairment is not pertinent to this discussion. In these cases of carbon tetrachloride nephrosis the severe oliguria or anuria likewise prevented a satisfactory excretion of sodium and water, while renal extraction studies disclosed that, as in the usual cases of congestive heart failure, the renal blood flow was greatly diminished.[21] The deficient excretion of sodium and chloride is due chiefly to the quantitative reduction in urine volume. There is also a pronounced diminution in the actual concentration of sodium and chloride in the urine which is excreted.

There is some tendency to regard the pulmonary and generalized edema and the associated clinical phenomena as manifestations of overhydration with administered fluids, as distinguished from congestive heart failure. This distinction appears unjustified for two reasons: First, the clinical features in these cases of carbon tetrachloride nephrosis were identical with those of classic congestive heart failure, as detailed above. Second, the congestive heart failure with primary cardiac disease is no less due to excessive intake and retention of sodium and water than is the congestive heart failure associated with nephrosis and urinary suppression.

Diffuse edema may be induced, even in normal individuals, by the ingestion of sodium and water, but only with quantities which greatly exceed the usual range of sodium-water intake. The essential distinction between congestive heart failure and the overhydration of normal individuals is the occurrence of the clinical features of heart failure when the intake of sodium and water is within the normal range. The normal individual usually ingests 5 to 15 gm. of sodium chloride daily and may

develop edema with daily intakes exceeding 25 gm. Patients with congestive heart failure maintain their edema or develop a recurrence of edema and other symptoms with daily intakes of 5 to 10 gm. and sometimes even with intakes as low as 2 gm. That the sodium intake is excessive is indicated by a positive sodium balance; that it is partly responsible for the edema and other symptoms may often be demonstrated by the disappearance of symptoms when the daily intake of sodium chloride is reduced to less than 1 gm. The development of edema in normal patients with an excessive intake of sodium and in cardiac patients with a normal intake of sodium is analogous to the occurrence of dyspnea in normal individuals with excessive effort and in cardiac patients in heart failure even with ordinary activity. The role of the normal sodium intake in the formation of edema or of ordinary activity in the production of dyspnea does not minimize the basic importance of cardiac failure.

In terms of these considerations the patients whose case histories have been described above correspond to patients with classic heart failure and not to normal persons overhydrated by ingestion of enormous quantities of sodium and fluid. Like patients with congestive heart failure of cardiac origin, those with lower nephron nephrosis suffer from dyspnea, edema, elevated venous pressure, etc., when their intake of sodium and water is in a quantitative range which can be absorbed by normal individuals without the development of symptoms.

*Treatment.* In the presence of severe oliguria and renal insufficiency treatment may be concerned with control of (1) azotemia, (2) acidosis, (3) hypochloremia, (4) hyperkalemia or (5) congestive heart failure. The measures designed to alleviate some of these abnormalities are unsuitable or detrimental to others. Treatment should be designed primarily to prevent congestive heart failure for this is the complication which is most apt to endanger life.

Azotemia has been used as the chief guide to renal function in these cases and most therapeutic measures have been designed to combat this abnormality. In the cases of lower nephron nephrosis due to carbon tetrachloride, and in most other etiologic types of this condition, resumption of excretion usually commences on the tenth to the fourteenth day after exposure and the fall in blood urea usually commences after the fifteenth day. Available evidence indicates that death does not occur from uremia as such during this brief period. Therefore, measures to reduce azotemia are justifiable only if they are not fraught with risk and if they do not interfere with measures designed to prevent or alleviate heart failure.

Acidosis associated with the oliguria and azotemia is a second abnormality which frequently impels the physician to the administration of sodium-containing fluids. Yet the degree of acidosis observed in these cases is not as severe as that usually present for long periods of time in cases of chronic nephritis. The serum phosphorus was usually less than 5 mg. per cent and the carbon dioxide combining power was only moderately diminished. There is little risk from acidosis of such degree for the limited period before spontaneous correction.

Hypochloremia is likewise of moderate degree during the oliguric period of ten to fourteen days. The reduction in concentration of plasma sodium and chloride is partly due to dilution by disproportionately increased extracellular fluid retention and partly to mild acidosis with intracellular-extracellular shifts of electrolytes and water. The danger of hypochloremia arises when profound diuresis begins and large quantities of chlorides and presumably sodium may be excreted. This may occur in other forms of lower nephron nephrosis, such as that due to intravascular hemolysis of erythrocytes,[22] but has not been observed in our cases of carbon tetrachloride nephrosis. In fact the concentration of plasma chlorides tended to rise as diuresis resulted in a proportionately greater excretion of water.

The concentration of potassium is often

elevated in all forms of uremia but only rarely to dangerous levels unless potassium salts are administered. Isolated determinations in the cases reported above revealed only slight increases in potassium concentration, and the electrocardiographic abnormalities associated with pronounced hyperkalemia were not observed. However, this is a distinct possibility and like pulmonary edema may be a cause of death. For this reason repeated determinations of serum potassium are desirable. Electrocardiograms, taken every other day, should provide an adequate clue to significant hyperpotassemia. With potassium levels in excess of 6 mEq./L. the T waves become tall and peaked. With levels above 8 or 9 mEq./L., auriculoventricular and intraventricular block occur and the P waves are lowered. Ventricular fibrillation and cardiac arrest are apt to occur when the serum potassium level exceeds 13 mEq./L. While the best treatment for hyperpotassemia in lower nephron nephrosis has not been defined, the use of the artificial kidney with a perfusion fluid low in potassium or exsanguination transfusion should be considered.

*Limitation of Sodium and Fluid Intake.* It is probable that the reduction in intake of sodium in carbon tetrachloride (lower nephron) nephrosis is more important than extreme fluid restriction, just as it is in the treatment of congestive heart failure. The indication for sodium restriction is even more acute and the degree of sodium restriction should be more extreme than in most cases of ordinary congestive heart failure, since the output of sodium in the former is virtually zero whereas in most cases of ordinary congestive heart failure sodium excretion is merely impaired.

Reference has already been made to the probable importance of sodium even in small quantities in the induction of heart failure. In a case of carbon tetrachloride nephrosis which I observed only briefly and which is not included in the above series the patient on admission presented distention of the cervical veins, hydrothorax, a tender enlarged liver and mild peripheral edema although his fluid intake average was only 1,150 cc. daily in the two days preceding admission. However, he had been given 28 gm. of sodium chloride in that period. In the next forty-eight hours his total fluid intake was only 1,400 cc. orally yet at the end of that period he was in frank pulmonary edema which was obvious on clinical and roentgenologic examination, and he had to be phlebotomized. Although the small quantities of fluid ingested may be eliminated by insensible perspiration, the sodium has less egress and may increase extracellular fluid by withdrawing fluid from the cells. Similarly in case 3 above, heart failure present on admission had been controlled on an intake of less than 500 cc. daily and no sodium. But because of pronounced hyponatremia the patient was given 12 gm. of sodium chloride in twenty-four hours without change in fluid intake. This was followed by acute pulmonary edema.

As a rule, then, no sodium should be administered in any form until diuresis is established, i.e., until about the end of the second week or beginning of the third week after exposure to carbon tetrachloride. An exception may have to be made at the onset of lower nephron nephrosis when associated with severe hemorrhage or shock in which a pronounced depletion of circulating blood volume is clearly demonstrable.

The problem of fluid restriction is more complex. In the conventional cases of congestive heart failure a moderate fluid intake is permissible and even desirable if the sodium intake is minimized. The aim is to provide enough fluid for the renal excretion of sodium as well as of other waste products.[23] But in the cases of nephrosis with oliguria or anuria no such excretion occurs and whatever fluid is administered, with or without sodium, is virtually all retained. Thus the clinical features of congestive heart failure in lower nephron nephrosis usually develop with fluid intakes between 1,500 and 2,500 cc. daily and occasionally with intakes of approximately

1,000 cc. or even less. The fluid allowance must often be varied according to the fluid intake in the first few days of the nephrosis when the patient has been treated elsewhere. To allow for insensible perspiration 500 to 1,000 cc. of fluid, without sodium, is usually permitted daily during the period of extreme oliguria. But this allowance, as indicated previously, may have to be modified in certain types of lower nephron nephrosis if when the patient is first seen there is overt evidence of an inadequate cardiac output or shock due to a severe reduction in circulating blood volume. In the cases of carbon tetrachloride nephrosis reported above the patients when first seen had already been overhydrated with quantities of fluid not justified by any deficient blood volume. Under such circumstances it is safer to reduce the fluid intake to the barest minimum and certainly to not more than 500 cc. The extent of overhydration in these cases was indicated by the rapid diuresis of 10 to 25 pounds of fluid within a few days when recovery ensued.

*Digitalis.* The administration of digitalis is to be considered only if manifestations of congestive heart failure appear. In the absence of evidence of myocardial damage as the basis of the "heart failure" syndrome the indication for digitalis is uncertain. Furthermore, in the presence of anasarca and severe oliguria there is danger of delayed elimination and of sudden flooding of the tissues with digitalis when diuresis begins. If digitalis is administered, rapidly eliminated digitalis glycosides appear to be preferable in these cases, e.g., cedilanid for parenteral and digoxin for oral use.

Mercurial diuretics, urea and acidifying salts are contraindicated in view of the renal damage, azotemia and acidosis already present.

*Phlebotomy.* If acute pulmonary edema develops, usually because of the excessive administration of sodium-containing fluids, morphine, oxygen, tourniquets and rapid digitalization may afford relief but phlebotomy should not be too long delayed if these measures are ineffective.

*Food Intake.* It is desirable to maintain caloric balance and to prevent the excessive endogenous breakdown of cellular protein. However, adequate oral intake is not always feasible because of anorexia or vomiting while intravenous feeding may be dangerous if it necessitates the simultaneous introduction of sodium and fluids. As a rule the oral intake should consist at first only of fruit juice, fruits and rice. Glucose solutions are preferred if parenteral feedings are necessary. Since the duration of the illness before spontaneous diuresis is relatively brief, maintenance of caloric balance is permissible only insofar as it does not demand a compromise with the risk of heart failure and acute pulmonary edema.

## SUMMARY AND CONCLUSIONS

1. Four cases of lower nephron nephrosis due to carbon tetrachloride are reported from the viewpoint of associated congestive heart failure.

2. Attention is directed to the frequency with which pulmonary edema and the classic manifestations of congestive heart failure are induced in these patients with urinary suppression by efforts to promote diuresis or to correct acidosis, hyponatremia or hypochloremia.

3. It is emphasized that the congestive heart failure syndrome appears not only after massive intake of fluids but even with moderate quantities of fluid and especially after relatively small amounts of sodium.

4. Because congestive heart failure is the most serious complication and the one most apt to cause death during the period of oliguria, treatment should be devoted primarily to the avoidance or control of this complication. Azotemia, acidosis, hypochloremia and hyponatremia in these cases are either of too brief duration or too mild to be dangerous and moreover disappear when spontaneous diuresis occurs on the tenth to the fourteenth day after exposure.

5. The extreme reduction or complete absence of renal excretion of sodium and fluids demands a correspondingly extreme

restriction in sodium and fluid intake until diuresis is established. Cautious modification of this regimen may be necessary if there is a reduction in circulating blood volume due to hemorrhage or in other types of lower nephron nephrosis associated with severe hemorrhage and shock or uncorrected reduction in blood volume or salt depletion.

6. The occurrence of the complete clinical picture of congestive heart failure as a result of sodium and water retention due to pure renal disease without evidence of cardiac disease supports the concept that renal dysfunction is also responsible for the clinical phenomena of heart failure when the primary disease is in the heart.

REFERENCES


1. Lucké, B. Lower nephron nephrosis. *Mil. Surgeon*, 99: 371, 1946.
2. Bywaters, E. G. L. and Beall, D. Crush injuries with impairment of renal function. *Brit. M. J.*, 1: 427, 1940.
3. Maegraith, B. G., Havard, R. E. and Parsons, D. S. Renal syndrome of wide distribution induced possibly by renal anoxia. *Lancet*, 2: 293, 1945.
4. Peters, J. T. Oliguria and anuria due to increased intrarenal pressure. *Ann. Int. Med.*, 23: 221, 1945.
5. Franklin, K. J., Barclay, A. E., Daniel, P., Trueta, J. and Pritchard, M. M. L. Renal pathology in the light of recent neurovascular studies. *Lancet*, 2: 239, 1946.
6. Corcoran, A. C. and Page, I. H. Crush syndrome: post-traumatic anuria. *J. A. M. A.*, 134: 436, 1947.
7. Van Slyke, D. D. The effects of shock on the kidney. *Ann. Int. Med.*, 28: 701, 1948.
8. Abeshouse, B. S. Renal decapsulation: a review of the literature and a report of ten cases. *J. Urol.*, 53: 27, 1945.
9. Fine, J., Frank, H. A. and Seligman, A. M. The treatment of acute renal failure by peritoneal irrigation. *Ann. Surg.*, 124: 857, 1946.
10. Kolff, W. J. New Ways of Treating Uremia. London, 1947. J. & A. Churchill, Ltd. The artificial kidney. *J. Mt. Sinai Hosp.*, 14: 71, 1947.
11. Oppenheimer, G. D. and Rosenak, S. Intestinal irrigation in the treatment of certain types of uremia. *J. Mt. Sinai Hosp.*, 14: 908, 1948.
12. Snapper, I. Management of acute renal failure. *Bull. New York Acad. Med.*, 25: 199, 1949.
13. Muirhead, E. E., Vanatta, J. and Grollman, A. Acute renal insufficiency. A comparison of the use of an artificial kidney, peritoneal lavage and more conservative measures in its management. *Arch. Int. Med.*, 83: 528, 1949.
14. Stock, R. J. Acute urinary suppression. *Am. J. Med.*, 7: 45, 1949.
15. Kugel, V. H. Management of acute toxic nephrosis. *Am. J. Med.*, 3: 188, 1947.
16. Burnett, C. H. Clinical and therapeutic aspects of acute renal insufficiency due to lower nephron or hemoglobinuric nephrosis. *Am. Pract.*, 2: 6, 1947.
17. Muirhead, E. E. and Fromm, C. S. Severe acute renal insufficiency. *J. A. M. A.*, 137: 1378, 1948.
18. Strauss, M. B. Acute renal insufficiency due to lower nephron nephrosis. *New England J. Med.*, 239: 693, 1948.
19. Hoffman, W. S. and Marshall, D. Management of lower nephron nephrosis. *Arch. Int. Med.*, 83: 249, 1949.
20. Friedberg, C. K. Diseases of the Heart. Philadelphia, 1949. W. B. Saunders Co.
21. Sirota, J. H. Carbon tetrachloride poisoning in man. I. The mechanisms of renal failure and recovery. *J. Clin. Investigation*, 28: 1412, 1949.
22. Thorn, G. W. Treatment of renal insufficiency. *J. Urol.*, 59: 119, 1948.
23. Gorham, L. W., Lester, D. E., Wolf, A. V. and Shultz, H. H. The relative importance of dietary sodium chloride and water intake in cardiac edema. *Ann. Int. Med.*, 27: 575, 1947.

# Chronic Obstruction of Major Pulmonary Arteries*

DOUGLAS CARROLL, M.D.
*New York, New York*

MASSIVE obstruction of major pulmonary arteries results most frequently from embolism or thrombosis.[1] Death usually occurs before the development of chronic cor pulmonale. When patients do survive massive obstruction of major pulmonary arteries, however, the clinical picture is characterized by cyanosis, dyspnea, orthopnea, polycythemia, right-sided heart failure and right axis deviation of the electrocardiogram. Physical and radiologic examination of the heart and lungs may reveal little of note and establishing the diagnosis during life may be extremely difficult.

Five cases of chronic cor pulmonale resulting from obstruction of pulmonary arteries have been encountered recently. One case appears to have resulted from local thrombosis, the others from embolism. Together they provide useful information regarding the pathogenesis of this unusual process.

## CASE REPORTS

CASE I. (Johns Hopkins Hospital, History No. 382,445.) A thirty-five year old married Negro veteran entered the hospital on November 26, 1946, complaining of shortness of breath, cough and bloody sputum of two years' duration. In January, 1943, the Wassermann reaction of his serum was negative. Following a penile lesion in 1944 he had a positive Wassermann reaction and was treated with 2,400,000 units of penicillin. In October, 1945, his Wassermann reaction was negative. In 1944 he had an appendectomy without complication.

His present illness started in 1944 with sudden onset of pain in the left side of the chest made worse by breathing. He was treated in a hospital for three weeks and discharged improved. The pleurisy recurred on the left eight months later, lasting for three days. Subsequently he had recurrent minor episodes of pleuritic pain. Dyspnea on exertion began in December, 1945. This was followed by an episode of severe paroxysmal nocturnal dyspnea. Shortly thereafter he fainted after running upstairs. From then on he experienced mild exertional dyspnea and intermittent orthopnea. In January, 1946, he noticed soreness and swelling of his right leg with increasing dyspnea and recurrence of the pain in his chest. This led to hospitalization for six weeks with improvement in his symptoms without specific treatment with digitalis, oxygen or diuretics. On discharge there was some dyspnea on exertion; orthopnea returned and there was intermittent swelling of both legs, particularly on the right. He had mild episodes of pleurisy during the next month. Exacerbation of the orthopnea, dyspnea and ankle edema led to a second hospitalization in August, 1946. He was given digitalis and diuretics. He improved enough to return home. Three days before admission to the Johns Hopkins Hospital he noticed the onset of cough, blood-tinged sputum, chilly sensations and severe night sweats with increasing dyspnea and orthopnea.

On physical examination the temperature was 99°F., pulse 72 and respirations 24 per minute; blood pressure was 118/85. No cyanosis, icterus, petechiae or rash were noted. The veins of the arms and neck were tightly distended. There was slight edema of the ankles. Fine and medium inspiratory rales were heard under the right clavicle and high in the right axilla. A few coarse rhonchi were heard over the right base but no pleural friction rub was present. The heart percussed 10 cm. to the left in the fifth interspace and 3 cm. to the right in the fourth interspace. Marked sinus arrhythmia, prema-

* From The Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Md.

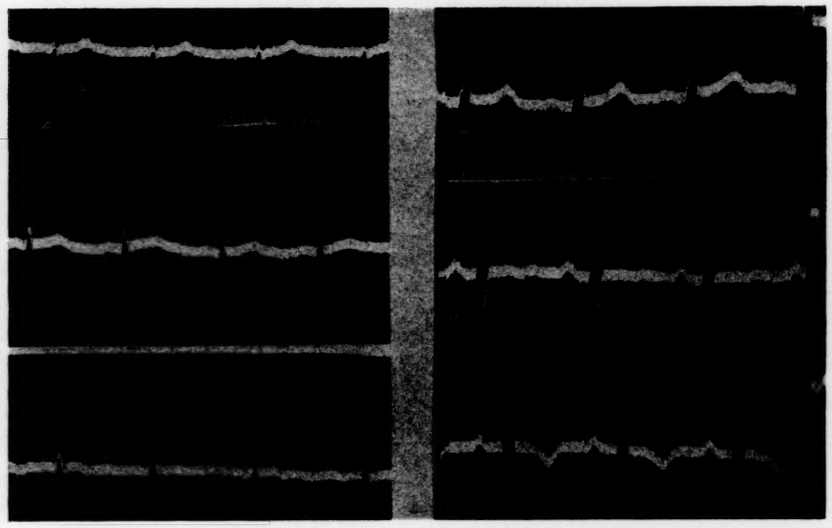


FIG. 1. Case 1. Development of right axis deviation; first electrocardiogram taken February 16, 1946; second electrocardiogram taken May 15, 1946.

ture beats and paradoxical pulse were present. At the apex the first sound was loud and merged into a systolic murmur. The second pulmonic sound was loud and split and exceeded the second aortic sound in intensity. A protodiastolic gallop was present in the fifth interspace just to the left of the sternum. The abdomen was tense and distended; ascites was present. The liver was felt 3 cm. below the costal margin both on the right and the left. The right leg was obviously larger than the left; its circumference at the calf was 1.5 cm. greater than the left. The calf was not tender on compression of the calf or dorsiflexion of the ankle.

The blood serologic test for syphilis was negative. The hematocrit was 52 mm.; hemoglobin was 16 gm., and the red blood count was 5.3 million per cubic mm. The sedimentation rate was 13 mm. per hour corrected by the Wintrobe method. The leukocyte count was 9,840 with a normal differential count. No sickle cells developed in the wet smear after twenty-four hours. Leukocyte counts on eight occasions gave values between 8,000 and 12,900. The urine was clear. The serum bilirubin was 3.7 mg. per cent total, with a direct reaction of 2.3 mg. per cent. The bromsulfalein test showed 5.2 mg. per cent retention in thirty minutes (5 mg. per kg. body weight). A type I pneumococcus was recovered from a mouse which had been injected with the sputum. Blood and throat cultures showed type I pneumococcus. The prothrombin time was 29 seconds or 40 per cent of normal; venous pressure was 235 mm. of saline.

An x-ray on admission showed consolidation in the right upper lobe. The patient was treated with 100,000 units of penicillin every two hours. It was thought possible that he might have rheumatic valvular disease with bacterial endocarditis superimposed. The possibilities of tricuspid disease and a localized constrictive pericarditis were entertained but neither could be supported from radiologic examination. The venous pressure remained elevated between 200 and 250 mm. of saline. The electrocardiogram showed that right axis deviation had developed since a previous electrocardiogram taken several months previously. (Fig. 1.) He was given oxygen, morphine and an initial dose of 0.3 gm. digitalis but responded poorly. An x-ray of the chest taken on the second day showed partial clearing of the right upper lobe. The temperature fluctuated between 100° and 101°F. during the first week. Because anorexia and coupled beats developed on the third day, digitalis was discontinued for the next four days. He was given vitamin K in dosages of 9.6 mg. daily for six days because of hypoprothrombinemia. His condition remained unchanged. The temperature began to rise slightly at the beginning of the second week reaching 101° to 102°F. An attempt at diuresis with mercupurine was not successful. Phlebotomy of 450 cc. of blood gave striking relief for a period of about eight hours but dyspnea and orthopnea recurred, requiring constant oxygen. No diastolic murmur was heard throughout his hospital stay. On the night of the eleventh hospital day he became increasingly restless and dyspneic, and complained of severe pain in the right side of his chest. Subse-

quently he became comatose and cyanotic, and died shortly thereafter.

At autopsy the patient had slight edema of the dorsum of the right foot. There were 900 cc. of ascitic fluid; no pleural fluid was present. The main pulmonary artery was free of obstruction but each pulmonary branch was obstructed by thrombus material in different stages of organization. There were numerous areas of infarction of the lung. The freshest infarct, located in the right upper lobe, was wedge-shaped with a soft necrotic area near the periphery. The heart weighed 400 gm. The right ventricle measured 0.8 cm. in thickness and the left ventricle 1.5 cm. The tricuspid valve measured 13 cm., the pulmonary valve 7.5 cm., the mitral valve 9.5 cm. and the aortic valve 6 cm. In addition to the hypertrophy of the right ventricle, there was also dilatation. The liver was nutmeg in appearance and weighed 1,700 gm. A section of the right femoral vein showed a remnant of an organized recanalized thrombus.

*Comment.* This patient is an example of the development of cor pulmonale secondary to repeated emboli to large pulmonary vessels. His episodes of pulmonary embolism were followed by increasing dyspnea. Physical examination showed evidence of right heart failure. Little was found in the physical and x-ray examinations of the lungs to explain the right-sided failure. He had polycythemia, right axis deviation by electrocardiogram and a poor response to digitalis. At autopsy the cor pulmonale was thought to be due to the obstruction to the pulmonary arteries by emboli. The origin of the emboli was thought to be in the right femoral vein where a recanalized thrombus was present.

Case II.* (Bellevue Hospital Chest Service, History No. 53,522.) A forty-one year old white female entered Bellevue Hospital for the first time March 10, 1947, complaining of dyspnea of seven months' duration. Her present illness started in February, 1946, with swelling and tenderness of the left leg, without antecedent trauma. She was thought to have thrombophlebitis of the left leg and was treated with penicillin and sulfadiazine. After nine weeks there was still slight edema of the left leg on standing. In July, 1946, swelling and pain began in the right leg and lasted about two weeks, leaving slight edema of this leg also on standing.

On August 3, 1946, while lifting a small can of ashes, she was seized with sudden dyspnea, orthopnea and a non-productive cough. She remembered no pain in the chest or hemoptysis. Four days later she went to a hospital because of pain in the right upper leg. Except for slight ankle edema, physical examination on admission was not remarkable. Her dyspnea and orthopnea increased on bed rest. Early in October, 1946, a transitory friction rub was heard at the left apex and shortly thereafter a systolic murmur appeared over the precordium for the first time. The liver was felt down 5 cm. at this time. Dorsiflexion of the right foot produced pain in the right calf. The blood pressure remained around 140/100. A chest x-ray on October 5th showed a well circumscribed cavity in the left mid-lung field. Circulation time with decholin was 12 and 20 seconds on two occasions. Venous pressures were 290 mm. and 220 mm. of saline. On October 28th tachycardia and a gallop rhythm were present and the heart was noted to be enlarging. She was digitalized with no apparent effect and discharged in December, 1946, without improvement in her dyspnea and orthopnea. At discharge the chest x-ray showed the cavity surrounded by an area of density.

Because of increasing dyspnea she entered a second hospital in January, 1947. At this time she was dyspneic and cyanotic. Her blood pressure was 170/100. Rales were present in the left axilla and a loud systolic murmur was heard in the third and fourth interspace to the left of the sternum. The second pulmonic sound was accentuated. The liver was not enlarged. Leukocyte counts were 11,000 and 15,000 with normal differential counts. Hemoglobin and erythrocyte values were normal. Venous pressure was 110 mm. of saline. Circulation times with decholin were 11 and 15 seconds. Digitalization did not relieve her symptoms for the second time. She was discharged undiagnosed on February 4th.

Because of increasing dyspnea and orthopnea, she entered Bellevue Hospital for the first time on March 10, 1947. She had lost 65 pounds weight and had noted curvature of her fingernails. On admission her temperature was 99.2°F., pulse 100, and respirations 40 per minute; blood pressure was 142/88. She was dyspneic, cyanotic and orthopneic. There was evidence of marked

* Thanks are due to Doctor J. Burns Amberson for the use of this case.

weight loss. The venous pressure was increased clinically. The trachea was deviated slightly to the left and there was lag in expansion of the left chest. Breath sounds were decreased over the entire left chest posteriorly. A few post-tussic rales were noted in the left infraclavicular area. The heart was enlarged with the point of maximal impulse in the fifth interspace just inside the left anterior axillary line. The second pulmonic sound was greater than the second aortic sound. There was a loud precordial systolic murmur. The liver was felt down 7 cm. below the costal margin. There was cyanosis of the nail beds with clubbing. There was slight edema of both ankles but no pain was present on dorsiflexion of the feet.

The serologic test for syphilis was negative. Leukocyte counts were 12,900 and 10,300. The hematocrit was 42 mm.; venous pressure was 150 mm. of saline. An ether circulation time, arm to lung, was five seconds, and a decholin circulation time, arm to tongue, was thirteen seconds. The chest x-ray showed that the heart was increased in transverse diameter. There were discrete fine markings throughout the right lung field. The electrocardiogram showed normal axis with inversion of the T wave in Leads III, $CF_1$, $CF_2$, $CF_3$ and diphasic T waves in Leads II and $CF_4$.

Her temperature varied between 98.6° and 100.2°F. Sputum was scanty but she had a persistent cough and was quite orthopneic. She was thought to have a chronic lung abscess secondary to a septic infarct. The changes in her lungs, however, were thought insufficient to explain her severe dyspnea and orthopnea. On March 31st, studies were carried out under the direction of Dr. André Cournand. The right heart was catheterized and pulmonary artery pressure was found to be 96/36. The cardiac output was 2.44 L. per minute per square meter body surface. She was again digitalized and felt slightly improved. On April 12th she was discharged on a low salt diet and digitalis.

She did fairly well on bed rest at home until the night on May 4th when her dyspnea and cough greatly increased. She began to hear voices telling her that there were spies in her room. She was brought to Bellevue Hospital on May 7th. She had lost 11 pounds since discharge and was disoriented. Her temperature was 99.8°F., pulse 94 and respirations 36 per minute; blood pressure was 138/90. Otherwise her examination was the same as on the previous admission. On May 12th the electrocardiogram showed inversion of $T_1$ with depressed $ST_2$ and diphasic $T_2$. She remained severely dyspneic and had increasing edema. She had a small hemoptysis on August 4th. A friction rub was heard in the right mid-scapular line at the seventh rib. She refused to take medication. On October 3rd the electrocardiogram showed $T_1$ upright with a small $S_1$ and $T_{CF4}$ inverted. Rales appeared at the left base, and her condition became worse until she expired on October 23, 1947.

Autopsy showed an emaciated woman with edema to the sacrum. There was clubbing of the fingers. Both lungs showed extensive fibrous adhesions to the parietal pleura. The heart was hypertrophied on the right but not the left. The right ventricular wall averaged 1 cm. in thickness; the left ventricular wall measured 1.5 cm. Partially organized thrombi were attached to otherwise normal tricuspid and mitral valves. A well organized thrombus nearly occluded the left pulmonary artery and extended into the main pulmonary artery with partial obstruction. Section of the left lung showed almost complete excavation of the parenchyma. Patchy areas of necrosis remained. At the left apex several fibrocaseous lesions were present which showed tubercles with Langerhans' giant cells microscopically. In the right lung there was a wedge-shaped area of consolidation in the upper lobe extending to the pleural surface. A 2-cm. smooth-walled cavity was present in the right lower lobe. The liver weighed 1,520 gm. There were stones in the gallbladder. The kidneys were small, weighing 100 gm. each; the capsules stripped easily and the cortical architecture appeared normal. Dissection of the left femoral vein showed an old organized thrombus with small areas of recanalization.

Microscopic sections showed an organized thrombus attached to the wall of the main and left pulmonary arteries. The lungs showed patchy consolidation. The wall of the cavity in the left lung was thick and consisted of vascular fibrous connective tissue. A section from the right upper lung field showed hemorrhagic infarction with central alveolar septal necrosis. The wall of the cavity in the right lower lobe was thick and fibrous and contained no tubercles or Langerhans' giant cells.

There was passive congestion of the liver with scarring of the gallbladder. There was hyalinization of glomeruli with increased interstitial fibrosis just beneath the kidney capsules. The arteries in this area were thickened and partially hyalinized, and the tubules were pale and

granular. The left femoral vein showed an organized fibrotic thrombus with areas of recanalization lined by normal endothelium.

*Comment.* This patient had well recognized thrombophlebitis with repeated clinical episodes of pulmonary embolism. The venous pressure was elevated and a small $S_1$ appeared in her serial electrocardiograms. Frank right axis deviation and polycythemia never appeared. Her liver was greatly enlarged and she had ankle edema. The clubbing of her fingers was thought to be due to abscess formation secondary to breakdown of infarctions. The systolic murmur appeared at the time of a pulmonary embolus and may have been due to turbulence or increased blood flow in the right pulmonary artery. Dr. Cournand's studies showed a pulmonary artery pressure of 96/36 with a low cardiac output.

CASE III. (Johns Hopkins Hospital, History No. 465,364.) A forty-five year old white man entered the hospital on June 22, 1948, complaining of dyspnea of several weeks' duration. Although he was a chronic alcoholic, his health had been good until four months prior to admission. At this time he had a poorly described episode of unconsciousness lasting about twelve hours and followed by weakness on the right side of his body.

Two months before admission he had an acute attack of pain in the right chest with fever and blood-streaked sputum. The cough continued to be productive of blood throughout the next two months and was associated with dyspnea, fever, anorexia and weight loss. Because of the increasing dyspnea, he came to the hospital. Further details of the history were obscure because the patient was disoriented.

On physical examination the temperature was 101°F., pulse 110 and respirations 32 per minute. The blood pressure was 110/85. He was disoriented, orthopneic, restless, dehydrated, cyanotic and showed evidence of weight loss. There was clubbing of the fingers and toes. The teeth were carious. There was dullness to percussion in the left axilla, over the left apex and at the right base posteriorly. The breath sounds were distant at the right base. There were rales at the left apex and over most of the right chest. There was no increase in the venous pressure. The second pulmonic sound was louder than the second aortic sound. A loud blowing systolic murmur was heard in the fourth interspace just to the left of the sternum. The liver was felt down 4 cm. There was a right hemiplegia with weakness, wasting and spasticity of the right arm and leg. There was swelling and edema of the right leg.

Laboratory studies showed a negative Wassermann reaction. The erythrocytes were 5.45 million with a hemoglobin of 14 gm.; the hematocrit was 50 mm. The sedimentation rate was 11 mm. per hour corrected by the Wintrobe method. The leukocyte count was 21,900. The urine concentrated to 1.012, and there was 3 plus albuminuria. The spinal fluid was normal. A chest x-ray on admission showed the heart to be grossly enlarged with prominence of the pulmonary artery and increase in the vascular shadows. The costophrenic angle on the right was obliterated. There was infiltration of the left upper lung field.

The patient was given oxygen and intravenous fluids without improvement. On the second day his cyanosis increased and his blood pressure fell to 70/50. The administration of plasma did not improve his status. His temperature rose to 106°F. and he had a shaking chill. He expired soon after on the second hospital day.

Autopsy showed atrophy of the muscles of the right arm and leg with marked clubbing of the fingers and toes. The right leg was swollen and edematous. There was a thrombus in the right common iliac vein and the lower inferior vena cava. Microscopically, gram-positive cocci and rods could be seen in the thrombotic material surrounded by chronic inflammatory tissue. The lungs contained numerous white infarcts with central softening. There were numerous cavities in the right lower lobe, one of which was continuous with the pleural cavity. Microscopically the lungs showed thrombi and infarcts of all ages. Gram-positive cocci and rods were present in many of the infarcts with abscess formation. The pulmonary artery to the left upper lobe contained a large fragmenting thrombus extending into the main pulmonary artery, almost completely obstructing it. There were numerous thrombi in smaller branches of the left pulmonary artery. Microscopically the material in the large pulmonary vessels showed old, organizing thrombi with necrosis and many gram-positive cocci. Extensive recanalization was present in many of the thrombosed vessels.

The heart weighed 430 gm. The right ventricle was dilated and hypertrophied with an average wall thickness of 1.2 cm. The right auricle was dilated without hypertrophy. The left ventricle and auricle were normal. The valves were not remarkable. The foramen ovale was closed. Some grayish material, adherent to the right ventricular wall, proved microscopically to be an old organized infected thrombus. The liver weighed 2,050 gm. There was atrophy of the central cells of the liver. The spleen weighed 160 gm. and had the characteristics of an acute splenic tumor. There was complete obstruction of the left common carotid artery by an organized thrombus. The brain showed atrophy of the left anterior temporal region.

*Comment.* There was little in this patient's history to suggest pulmonary obstruction. The hemiplegia and signs of infection in the lungs obscured the diagnosis. He died on the second hospital day in shock with high fever. At autopsy he presented extensive thrombosis of major pulmonary arteries extending into the main pulmonary artery with severe obstruction to the circulation.

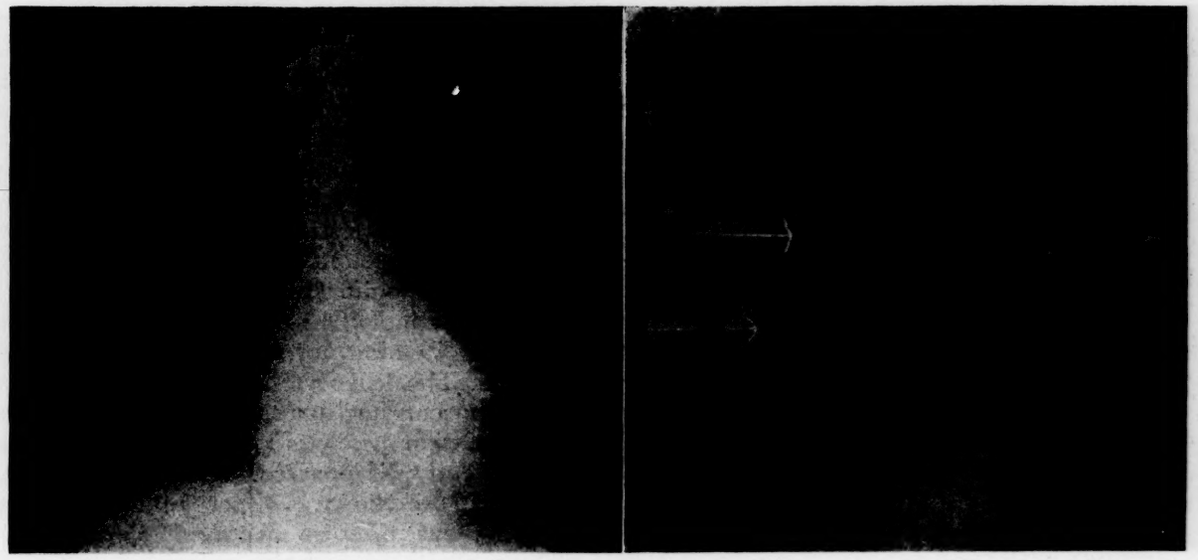
CASE IV. (Johns Hopkins Hospital, History No. 441,754.) This thirty year old, white man of Italian extraction was admitted to the hospital complaining of weakness and fatigue of three years' duration. His present illness started in September, 1945, with ingravescent weakness and fatigue. In February, 1946, he stopped work entirely because of fatigue and dyspnea. In November, 1946, following an acute attack of abdominal pain, an acutely inflamed appendix was removed without postoperative complications. There was no thrombophlebitis. In January, 1947, he first experienced orthopnea and ankle edema with increasing exertional dyspnea. About this time his first episode of syncope occurred several minutes after lifting his child out of the bathtub. Subsequently he had three or four similar episodes after straightening up from a stooping position.

In March, 1947, he entered the Mary Imogene Bassett Hospital complaining of exertional dyspnea. His blood pressure was 112/80. His lungs were clear. The heart was enlarged to the left and there was a rough systolic murmur over the aortic and mitral area. The liver was 5 cm. below the costal margin and was not tender. There was pitting edema of the lower extremities. He responded well to digitalis. Following discharge he began to have nocturnal dyspnea and edema returned. He was rehospitalized in cardiac failure and improved on a low salt diet, digitalis, ammonium chloride and mercupurine.

On June 18, 1947, the patient had an episode of sharp pain in the left anterior chest made worse by respiration. The following morning he noted slightly blood-streaked sputum. He was thought to have had a small pulmonary embolus. He was examined on September 3, 1947, by Dr. James Bordley who noted a curious murmur over the right side of the back. He was admitted to the Johns Hopkins Hospital on December 5, 1947, for further studies.

On physical examination the temperature was 98°F., pulse rate 92 and respirations 28 per minute. The blood pressure was 106/76. He was well developed, well nourished and slightly orthopneic. The lips and tongue were cyanotic and there was definite icterus. There was moderate pitting edema of the hips and sacrum. The thyroid was diffusely enlarged with palpable nodules in the lateral lobes. The distention and pulsation of the cervical veins were very striking. The venous pulsation was systolic, obliterating the normal pulse waves. The left border of cardiac dullness was 16 cm. to the left in the fifth interspace. The point of maximal impulse was diffuse. The second pulmonic sound was louder than the second aortic sound. A loud systolic murmur was heard over the entire precordium, loudest just inside the apex and transmitted into the neck vessels. A systolic murmur was audible over the posterior right chest, especially loud in the right interscapular region, and fading out toward the right base. The lungs were entirely clear. There was moderate ascites. The liver was firm and palpable 5 cm. below the costal margin in the right mid-clavicular line. The spleen was not felt. There was no clubbing of the extremities.

The serologic test for syphilis was negative. The erythrocytes were 4.71 million with a hemoglobin of 15 gm.; the hematocrit was 49 mm. The sedimentation rate was 9 mm. corrected by the Wintrobe method. The leukocyte count was 7,520 with a normal differential. There was 1 plus albuminuria. The serum bilirubin was 3.5 mg. per cent with a direct reaction of 2.2 mg. per cent. The prothrombin time was twenty-six seconds. The thymol turbidity was 12 units and the cephalin flocculation test 4 plus. The venous pressure was 220 mm. of saline, and the circula-



2 3

FIG. 2. Case IV. Chest plate showing prominence of the pulmonary conus; the vascular markings are well seen in the right lung field but are absent in the left lung field.

FIG. 3. Case IV. Angiocardiogram taken twelve seconds after introduction of the opaque material; prominence of the pulmonary conus area is demonstrated. There is filling of the right pulmonary vascular tree but not of the left.

tion time (decholin) was twenty-five seconds. The electrocardiogram showed right axis deviation with diphasic $T_2$ and $T_{CF3}$. On digitalis and diuretics he had a satisfactory diuresis. Measurement of the legs following diuresis showed no significant difference in size at 10 cm. intervals.

Fluoroscopy of the chest showed that the principal enlargement was of the right auricle, with a normal-sized left auricle. The pulmonary arterial trunk was greatly enlarged. The right branch of the pulmonary artery could be clearly seen but the left branch did not appear on the film. (Fig. 2.) Right heart catheterization by Dr. Richard Bing showed the pulmonary arterial flow to be 1,750 cc. per minute per square meter of body surface. The pressure in the right ventricle was 80/20. It was concluded that there was no interventricular or interauricular septal defect. Angiocardiograms revealed the dye entering a large right auricle and then, slowly, an extremely large right ventricle. The right ventricle occupied the greater portion of the heart shadow. The pulmonary artery appeared somewhat larger than normal. A branch of the right pulmonary artery was visualized and was approximately normal in size. It divided into moderately sized trunks. The left pulmonary artery was not seen at any time and the left lung appeared to be almost entirely avascular. (Fig. 3.) The contrast solution reached the left side of the heart in about ten seconds which indicated definite delay. The left auricle was not enlarged. The impression was that there was a complete occlusion of the left pulmonary artery just below the bifurcation of the pulmonary trunk. The enlargement of the right ventricle and right auricle was believed to be secondary to the obstruction of the pulmonary vascular system. This obstruction was thought to have been caused by repeated pulmonary emboli.

Despite digitalis and diuretic therapy he gained weight, developed ankle edema and shortness of breath. On January 12th a left exploratory thoracotomy was performed under cyclopropane and ether anesthesia by Dr. Alfred Blalock. The left pulmonary artery was found to be exceedingly small with minimal pulsations. Aspiration of the main trunk of the left pulmonary artery revealed that blood flowed freely. The blood in the artery was bright red. Occlusion of the pulmonary artery peripheral to the needle, however, prevented the aspiration of any blood, indicating that there was complete obstruction between the heart and the needle. The main pulmonary artery was a very large dilated bulb. Because the left pulmonary artery was completely occluded, no objection was seen to dividing the artery. A biopsy of the left pulmonary artery revealed organized thrombi in the vessel. The patient withstood the operation surprisingly well. He had considerable dyspnea after the operation and his cyanosis did

not seem to improve. Postoperative vital capacity was 2.5 L. He was discharged unimproved.

*Comment.* This is the only patient of the series in which the diagnosis of cor pulmonale secondary to pulmonary embolism was made without autopsy confirmation. At operation, however, a biopsy of the left pulmonary artery showed it to be thrombosed. In addition the angiocardiograms showed no circulation of the radio-opaque material through the left pulmonary tree. The patient had episodes of pulmonary embolism. The murmur, which was loud and transmitted over the precordium and the right interscapular region, was thought to be due to diversion of the blood flow from the left pulmonary artery into the right pulmonary tree. Septal defects in this case were ruled out by heart catheterization and study of the blood gases. Dr. Bing's physiologic studies showed extremely high right ventricular pressure with a low cardiac output.

CASE V. (Johns Hopkins Hospital, History No. 374,863.) This forty-four year old, Negro laborer was admitted to the hospital on January 21, 1946, because of shortness of breath of two months' duration. He had pleurisy five years before admission without residua or recurrence. Five years before admission he had a penile lesion. At this time he was examined for military service and was told that he had syphilis. Although pronounced cured after eight injections, he was still rejected for military service for unknown reasons.

The present illness started suddenly two months before admission with exertional dyspnea. The dyspnea increased, occurring in episodes associated with palpitation, dizziness and vomiting. Three weeks before admission he began to have orthopnea and paroxysmal nocturnal dyspnea.

Physical examination on admission showed a temperature of 100.2°F., a pulse rate of 120 and respirations of 32 per minute. The blood pressure was 120/100. He was well nourished. He was dyspneic but not cyanotic. The veins of the neck on the right side pulsated markedly. The lungs were clear to percussion and auscultation. There was a diffuse apical impulse on the left beyond the mid-clavicular line. Cardiac dullness extended 11.5 cm. to the left in the sixth interspace and 5 cm. to the right in the fourth interspace. A triple rhythm was heard at the apex and there was a loud, harsh, systolic murmur. The second pulmonic sound was louder than the second aortic sound. The liver was felt 5 cm. below the costal margin and was slightly tender.

The serologic test for syphilis was negative. The red blood count was 4.14 million with 11.5 gm. of hemoglobin. The hematocrit was 39 mm., the icteric index 15 and the sedimentation rate was 19 mm. corrected by the Wintrobe method. The leukocyte count was 6,000. The urine concentrated to a specific gravity of 1.018. On admission there was 3 plus proteinuria which subsequently disappeared. The phenolsulphonphthalein excretion was 70 per cent in two hours. The venous pressure averaged 165 mm. of saline. The vital capacity was 2.7 L. Electrocardiograms showed slight right axis deviation. Serum non-protein nitrogen was 38 mg. %.

A chest x-ray revealed increase in the transverse diameter of the heart in both directions. The aorta was dilated and tortuous. The upper mediastinum was unusually widened with increased prominence of the superior vena cava and the right and left pulmonary arteries. There was increase in the hilar markings extending from the upper pole of the left hilus toward the apex. The septum, between the right upper and middle lobes, was thickened with an area of increased density seen below the fissure. The remainder of the right lung was essentially clear. There was increased mottling in the left upper lung field. There was asymmetry of the thoracic cage with narrowing of the interspaces on the right side.

His temperature ranged between 99° and 100°F. He was given digitalis and aminophylline but became progressively worse. A week after admission he had an attack of shortness of breath and faintness. His heart rate fell to 44 and the blood pressure to 95/60. Very soon his pulse was observed to quicken and it returned to a rate of 90 with improvement in the dyspnea and increase in blood pressure to 110/70. On the ninth hospital day he was found in extreme dyspnea as he was using the bed pan. The heart rate was forceful and regular at 48. He complained of no pain. While being put back in bed he became apneic and cyanotic. Supportive measures were unsuccessful and he died a few minutes later.

At autopsy no edema was noted. The circumferences of the legs were equal at 10 cm. inter-

vals above the ankles. The heart weighed 600 gm. and was enlarged due mainly to marked dilatation and hypertrophy of the right auricle and right ventricle. The tricuspid valve and pulmonic ring were greatly dilated. The left ventricle was slightly dilated and hypertrophied but this was inconspicuous compared to the great hypertrophy and dilatation of the right side. In the right pulmonary artery, and extending into its smaller branches, there was a yellow thrombus about 5 cm. in diameter which caused extreme dilatation of the arteries involved. Some of the smaller arteries were occluded. On the left there were smaller thrombi in the secondary branches of the pulmonary artery. In the right lower lobe there were at least two sharply outlined areas of infarction. The lungs were generally edematous. The liver weighed 1,700 gm. with some congestion. The blood was found to flow freely in the femoral veins and the iliac veins were not remarkable. Microscopic examination of the pulmonary artery at the site of the thrombus showed a dissection of the inner layer of the intima, thought to represent an ulceration in an intimal plaque. The media were not involved. The wall of the pulmonary artery and the adventitia were scarred and infiltrated. Many of the smaller branches of the pulmonary arteries contained thrombi. The lung alveoli were filled with edema fluid and there was syphilitic aortitis.

*Comment.* This patient represented the fully developed syndrome associated with thrombosis of the pulmonary vessels. There was increasing dyspnea with signs of failure of the right heart. T hephysical and x-ray findings in the chest were not sufficient clinically to explain the degree of dyspnea. Digitalis was of little help in relieving the patient's failure.

Autopsy showed a thrombus in the right pulmonary artery. There were infarctions in the right lung. The right side of the heart was greatly hypertrophied. An ulcerated intimal plaque in the right pulmonary artery was thought to represent the original site of thrombus formation.

## COMMENTS

*Differentiation of Pulmonary Embolism from in situ Thrombosis.* When an embolus lodges in a pulmonary artery, organization of the embolus follows rapidly. Thrombi may form around the embolus. By the time cor pulmonale has developed the embolus may no longer be recognizable pathologically. One is forced, therefore, to depend largely on the history of pleural pain, dyspnea and hemoptysis to be sure that the lesion found in the pulmonary vessel was embolic in origin. Hampden and Castleman[2] state: "Massive pulmonary embolism can occur in either or both main vessels with subsequent organization and superimposed thrombotic extension producing a cor pulmonale. Without a definite history of an embolic attack it would be almost impossible to differentiate this condition from a localized thrombus in the pulmonary artery."

In Case v there was no history to suggest recent pulmonary infarction. At autopsy a localized lesion in the pulmonary artery, on which a thrombosis could have occurred, was found. In this patient thrombosis was believed to have developed *in situ*. The first four patients, however, gave histories of episodes of pulmonary emboli so that embolic obstruction was thought to be the cause of their cor pulmonale.

*Cor Pulmonale Secondary to Pulmonary Emboli.* Three cases studied at autopsy have been reported in the literature and appear to be unquestionable examples of chronic cor pulmonale secondary to pulmonary emboli.[3–5] A fourth case, reported as an *in situ* thrombosis, may well have been secondary to an embolus.[6] These patients gave a history of leg pain or injury followed first by recurrent pulmonary embolism and later by chronic cor pulmonale. Injury was the probable cause of thrombosis in the extremities. Emboli originated from the thrombi. There was no evidence that the emboli originated in the right side of the heart. The episodes of pulmonary embolism were severe and were associated with pleural pain and bloody sputum in two cases. Symptoms of dyspnea, orthopnea and weakness usually followed soon after the attacks of pulmonary embolism. Examination at such times frequently showed the lungs to be clear. The cause of the symptoms, therefore, could not be attributed to heart failure. In one case signs of pulmonary

infection overshadowed the signs of embolism. Where reported, the electrocardiograms showed right axis deviation. Polycythemia was present where blood findings were given.

in which the pulmonary vessels were thoroughly investigated, thrombi were observed in twenty-eight cases. These thrombi usually involved smaller branches of the pulmonary artery. Occlusion of a main

TABLE I

CLINICAL AND LABORATORY FEATURES OF FIVE CASES OF CHRONIC PULMONARY ARTERY OBSTRUCTION*

| | Case I | Case II | Case III | Case IV | Case V |
|---|---|---|---|---|---|
| Age | 35 | 41 | 45 | 30 | 44 |
| Sex | M | F | M | M | M |
| History or findings of venous thrombosis of legs | +† | + | + | 0‡ | 0 |
| Embolic episodes | 5 | 2 | 1 | 5 | 0 |
| Dyspnea | + | + | + | + | + |
| Orthopnea | + | + | + | + | + |
| Paroxysmal nocturnal dyspnea | + | + | 0 | 0 | + |
| Cyanosis | 0 | + | + | + | 0 |
| Accentuated second pulmonic sound | + | + | + | + | + |
| Systolic murmur | + | + | + | + | + |
| Liver enlarged (cm.) | 3 | 7 | 4 | 5 | 5 |
| Ascites | + | 0 | 0 | + | 0 |
| Ankle edema | + | + | + | 0 | 0 |
| Hematocrit | 52 | 42 | 50 | 49 | 39 |
| Venous pressure | 250 | 150 | −§ | 220 | 165 |
| E.K.G. | Right axis deviation | Prominent $S_1$ | − | Right axis deviation | Right axis deviation |
| Clubbing | 0 | + | + | 0 | 0 |
| Benefited by digitalis | 0 | 0 | − | + | 0 |

* The obstruction in Cases I to IV was due to pulmonary embolism, while in Case V obstruction was due to an *in situ* pulmonary artery thrombosis.

† + means present.

‡ 0 means absent.

§ − means not done.

The time of survival following the first symptomatic pulmonary embolus varied from eight days to twenty-eight months. Digitalis and bed rest were of little help.

Table I summarizes the data on all the patients in the present report. Frank thrombophlebitis was the source of emboli in one patient. Cardiac murmurs were present in all cases. The degree of right-sided heart failure in two patients was very severe, resulting in ascites. Clubbing of the fingers was present in two patients; in one the pulmonary emboli were septic. The hematocrits were normal or high in all cases. Digitalis was given to three patients but was helpful in only one case.

*Cor Pulmonale Secondary to Thrombosis in situ.* Pulmonary thrombosis is not uncommonly found at autopsy. In Brenner's series[7] of one hundred unselected autopsies

pulmonary branch is unusual, and it is even more uncommon for the patient to survive long enough to develop cor pulmonale. Apparently lesions of the heart or pulmonary arteries which tend to cause congestion and slowing of the circulation in the pulmonary circuit favor the formation of thrombi in the pulmonary artery. Brenner states that mitral stenosis and patent ductus arteriosus, as well as local disease of the pulmonary arteries, such as arteriosclerotic plaques, syphilis, aneurysm and endarteritis, are commonly associated with thromboses of the pulmonary artery.

A few cases have been reported like Case V in which the thrombosis was secondary to a small lesion in the pulmonary artery with most of the symptoms and death resulting from the obstruction to the pulmonary artery. Means and Mallory[8] and others[9,12]

have reported such cases. The symptoms persisted over a long period of time; the picture was usually that described previously in recurrent emboli to the pulmonary artery, except that signs or symptoms of pulmonary embolus were lacking. In some cases to-and-fro murmurs over the pulmonary artery have been reported. In one case a thrombosed pulmonary artery threw a particularly dark shadow on the x-ray.[10] Savacool and Charr[11] and more recently Bryson[12] have reviewed the literature on pulmonary artery thrombosis.

Case v does not differ greatly from the cases reported in the literature except in his severe orthopnea and paroxysmal nocturnal dyspnea. He was not cyanotic and the hematocrit was not high.

*New Diagnostic Procedures and Findings.* Brenner has drawn attention to the difficulty in diagnosing thrombosis or embolism of the main lung arteries. He states: "Thus, in cases of thrombosis or chronic embolism of the main artery to one lung distinctive symptoms were unusual. In most instances the patient showed gradual progressive heart failure without a sudden onset, and the symptoms usually appeared either in the course of pre-existing heart failure or in patients in whom independent cardiac disease in itself made them liable to heart failure. Therefore, thrombosis can rarely be diagnosed." Means and Mallory,[8] however, conclude that cyanosis and right-sided heart failure without other obvious cause may suggest the presence of thrombosis of the pulmonary artery. Although the diagnosis may prove difficult, it can be suspected along with other causes of cor pulmonale.

In Case iv a new sign was observed in the chest x-ray which may be of help in making the diagnosis of complete obstruction of a pulmonary artery. This finding was the absence of vascular markings in the left lung field. A similar finding has been described in congenital heart disease.[13] This abnormality was also noted on the angiocardiogram. Murmurs may become audible while under observation and may have peculiar transmissions. Functional tricuspid insufficiency may develop. These findings may be evaluated by the technic of right heart catheterization. With the use of these newer technics the diagnosis of obstruction to major pulmonary arteries is simplified.

SUMMARY

Five cases of massive obstruction to pulmonary arteries with the development of chronic cor pulmonale are presented. Autopsy findings in four cases are available. One case was explored surgically and a biopsy of the pulmonary artery was made. The findings on right heart catheterization in two cases revealed high pressures with low cardiac outputs. Angiocardiography in one case demonstrated obstruction to the left pulmonary artery.

*Acknowledgment:* The author gratefully acknowledges the helpful advice and criticism given by Dr. A. McGehee Harvey and Dr. Joseph Lilienthal.

REFERENCES

1. Waring, James J. and Black, W. C. The syndrome of obstruction in the lesser circulation. *Am. J. M. Sc.*, 187: 652, 1934.
2. Hampton, A. O. and Castleman, B. Correlation of postmortem chest teleroentgenograms with autopsy findings. *Am. J. Roentgenol.*, 43: 305, 1940.
3. Barnes, Arlie R. and Yater, Wallace M. Failure of the right ventricle due to an ancient thrombus of the pulmonary arteries. *M. Clin. North America*, 12: 1603, 1929.
4. Belt, Thomas H. Late sequelae of pulmonary embolism. *Lancet*, 2: 730, 1939.
5. Meilman, Edward and Davison, Selvan. Pulmonary embolus of non-cardiac and non-postoperative origin. *J. Mt. Sinai Hosp.*, 11: 164, 1944.
6. Montgomery, G. L. A case of pulmonary artery thrombosis with Ayerza's syndrome. *J. Path. & Bact.*, 41: 221, 1935.
7. Brenner, O. Pathology of the vessels of the pulmonary circulation. *Arch. Int. Med.*, 56: 211, 457, 724, 976, 1189, 1935.
8. Means, J. H. and Mallory, T. B. Total occlusion of the right branch of the pulmonary artery by an organized thrombus. *Ann. Int. Med.*, 5: 417, 1931.
9. Covey, G. W. Chronic cor pulmonale with report of a case. *Ann. Int. Med.*, 18: 851, 1943.
10. Boswell, C. H. and Palmer, H. D. Progressive thrombosis of the pulmonary artery. *Arch. Int. Med.*, 47: 799, 1931.
11. Savacool, J. Woodrow and Charr, Robert. Thrombosis of the pulmonary artery. *Am. Rev. Tuberc.*, 44: 42, 1941.
12. Bryson, W. J. Propagating pulmonary artery thrombosis. *Dis. of Chest*, 15: 366, 1949.
13. Danelius, Gerhard. Absence of hilar shadow; diagnostic sign in rare congenital cardiac malformations. *Am. J. Roentgenol.*, 47: 870, 1942.

# Infections Resulting from Narcotic Addiction*

## *Report of 102 Cases*

HUGH H. HUSSEY, M.D. *and* SOL. KATZ, M.D.
*Washington, D.C.*

UNTIL 1943 the problem of narcotic addiction at the Gallinger Municipal Hospital was almost exclusively the concern of the psychiatrists. Occasionally a narcotic addict was seen in the medical or surgical division of the hospital, having been admitted because of an illness unrelated to his addiction. All other patients recognized as addicts were admitted to the psychiatric division. Some came to the hospital with the hope of overcoming their habit. The majority were brought to the hospital as a result of police action.

Since 1943, however, there has been a remarkable change, for as many narcotic addicts have been admitted directly to the medical or surgical services as to the psychiatric service. This change is the result of the high incidence of complications immediately related to the drug habit. The complications have been the prime concern in hospitalizing these patients.

Our purpose is to discuss the various medical and surgical complications resulting from addiction to heroin and morphine. These have included abscesses of the skin, thrombophlebitis usually with pulmonary infarction, septicemia, acute bacterial endocarditis, tetanus and malaria (Table I). From 1938 to 1947, inclusive, there have been 102 admissions to the hospital because of complications attributable to the use of narcotics; ninety-nine were heroin addicts and three were morphine addicts. It is obvious, therefore, that the problem of complications is almost entirely limited to heroin addicts. During this same period there were 263 admissions for uncomplicated addiction to opium derivatives: 104 morphine, 133 heroin, one pantopon and twenty-five combined. This makes the total incidence of complications 102 of 365 cases (28 per cent). However, the whole picture is not obtained until the incidence of complications is analyzed by years and by type of drug. (Figs. 1 and 2.) Whereas prior to 1943 complications were seldom seen (making up only 6 per cent of the total admissions), from 1943 through 1947 the incidence reached the imposing figure of 40 per cent. As was stated previously, the problem of complications is almost restricted to the heroin addicts; so when all cases of morphine addiction are excluded from the reckoning, the figures are indeed striking. Thus, from 1938 through 1942 there were seventy-eight admissions for heroin addiction of which seven were complicated (9 per cent), whereas from 1943 through 1947 the corresponding figures were 154 and

TABLE I
TOTAL COMPLICATIONS OF NARCOTIC ADDICTION IN 102 CASES

| Year | Uncomplicated Cases | Abscess | Thrombophlebitis | Septicemia | Endocarditis | Tetanus | Malaria |
|---|---|---|---|---|---|---|---|
| 1938 | 24 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1939 | 51 | 5 | 0 | 0 | 0 | 0 | 0 |
| 1940 | 13 | 2 | 0 | 0 | 0 | 0 | 0 |
| 1941 | 19 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1942 | 17 | 0 | 0 | 0 | 1 | 0 | 0 |
| 1943 | 18 | 2 | 0 | 2 | 3 | 1 | 0 |
| 1944 | 28 | 15 | 1 | 1 | 1 | 0 | 16 |
| 1945 | 21 | 10 | 0 | 1 | 1 | 5 | 6 |
| 1946 | 39 | 18 | 1 | 3 | 2 | 1 | 2 |
| 1947 | 33 | 16 | 2 | 0 | 0 | 0 | 5 |
| Totals | 263 | 68 | 4 | 7 | 8 | 7 | 29 |

* From the Georgetown Division of the Department of Medicine, Gallinger Municipal Hospital, and the Department of Medicine, Georgetown University School of Medicine, Washington, D.C.

ninety-two (59 per cent). The reasons for this marked increase in infections among heroin addicts after 1943 will be discussed hereafter. The influence of race on the incidence of complications is shown graphically in Figure 3. There was no important difference according to sex.

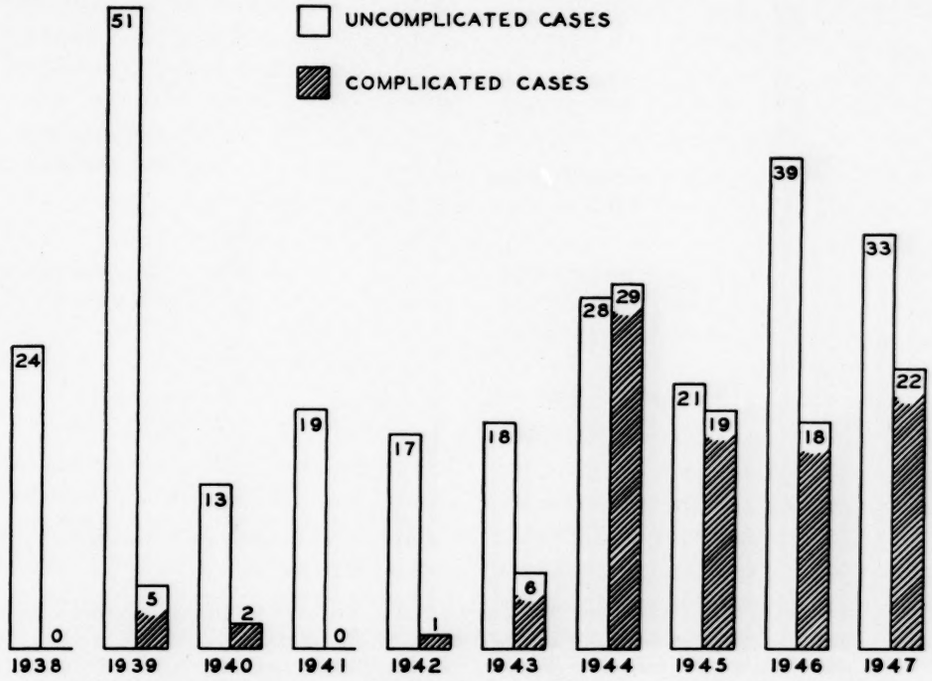


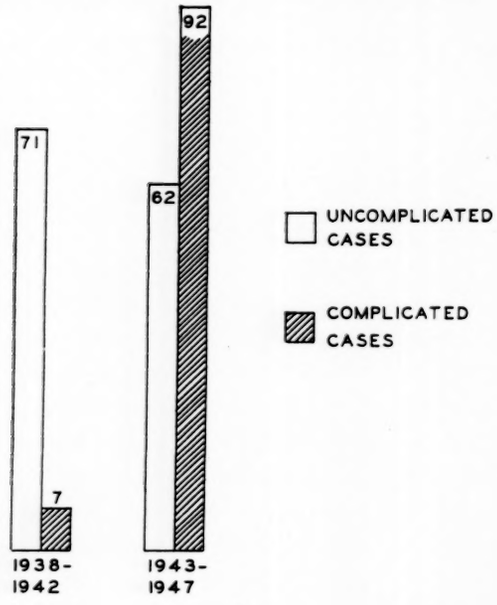

FIG. 1. Yearly incidence of complications in narcotic addicts, 1938 to 1947 inclusive.

A better appreciation of the mode of development of complicating infections in heroin addicts can be afforded by describing the methods used by the addicts in administering the drug. Most of the addicts we have treated for complications are Negroes in their twenties and thirties. It is their custom to meet in small groups as a social function. The heroin that they use has been adulterated by mixing with lactose or similar material; often the mixture contains barbiturates or cocaine also. Heroin is prepared by dissolving it in water with or without perfunctory boiling. A medicine dropper or 2-cc. syringe and hypodermic needle are used without previous sterilization. The material is usually injected intravenously. The equipment is passed from person to person in the group, being used repeatedly without sterilization. Skin antiseptics are not employed. These facts have an obvious relationship to the development of the various infections which are the subject of this paper. Contamination of the heroin, the use of an unsterile syringe and needle and the presence of bacteria on the skin all are potential sources for infection. In addition, the communal use of the equipment makes possible the transmission of infection from person to person.

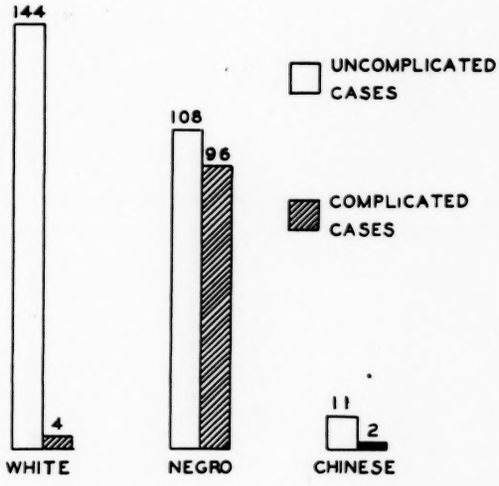
*Abscesses of the Skin.* Formation of skin abscess was the most frequent complication seen in narcotic addicts, occurring in sixty-eight cases, in all but two of which the drug used was heroin. Of this group, fifty had one or more abscesses, each located at a site of injection. There were eighteen additional cases in which such abscesses were accompanied with other complications such as thrombophlebitis (four cases), septicemia or septicopyemia (four cases), endocarditis (2 cases), tetanus (five cases) or malaria (three cases).

Many of the heroin addicts gave a history of having abscesses previously for which they did not receive hospital treatment. This fact supports the statement that this is

the most frequent complication encountered. The cases in which there were abscesses at the sites of injection and no other complication offered no problem in diagnosis or treatment. Chemotherapy, local application of heat and surgical drainage were successful in the treatment of this group. In the eighteen cases in which in addition to local abscesses there were other complications, the abscesses were a minor part of the problem. These cases will be discussed under the headings to follow.




2




3

FIG. 2. Contrast of incidence during two five-year periods of complications in heroin addicts.
FIG. 3. Incidence of complications of narcotic addiction by race.

*Thrombophlebitis.* Almost always the narcotic addict prefers to inject the drug intravenously, mainly because this technic affords a greater and quicker effect. As a result of continued abuse, the superficial veins of the arms and legs usually are thrombosed and cord-like. This appearance of the veins is one of the most constant stigmas of narcotic addiction and is therefore a helpful diagnostic finding. It has no other clinical significance except to interfere with venipuncture.

A more important type of venous disease is acute thrombophlebitis which was detected in four cases in this series. In all, abscesses had developed at sites of injection in the arms, and thrombophlebitis appeared as a consequence of extension of the inflammation to the local veins. In two cases there were obvious signs of the thrombophlebitis, as shown by swelling, induration, redness and tenderness along the course of the involved veins of the arm. There was also unmistakable evidence by x-ray of pulmonary infarction. Blood cultures were repeatedly positive for Proteus vulgaris in one of these cases. In the other two cases there was such extensive cellulitis and abscess formation of the arm that the condition of the local veins could not be evaluated. However, the diagnosis of thrombophlebitis was inferred from the detection by x-ray of pulmonary infarction.

Treatment in the cases of thrombophlebitis was essentially the same as in the group with abscesses of the skin. In addition, in the two cases in which the thrombophlebitis was obvious from the beginning, surgical ligation of the affected vein was performed. The pulmonary infarcts resolved without undergoing necrosis, and all patients recovered.

*Septicemia.* There were seven cases in which the clinical course and findings on

blood culture indicated a diagnosis of septicemia due to Staphylococcus aureus in six and Streptococcus viridans in one. In four instances there were abscesses at sites of injection as well as septicemia. In one of these thrombophlebitis and pulmonary infarction were additional findings, and have already been described herein. In another numerous metastatic cutaneous abscesses appeared during the course of the illness and obviously were in sites where heroin had not been injected although there was nothing to indicate the existence of visceral abscesses. In three cases there was septicemia without attendant abscesses. In one of these there was also malaria.

As might be expected, the clinical course in this group varied from moderately severe to very severe. All seven patients recovered. The mainstay of treatment was the use of antibiotics. In one case in which the patient was treated before penicillin was plentiful at this hospital, sulfadiazine was used effectively. In five cases penicillin was the curative agent. One of these patients also had malaria which required treatment with quinacrine. In the remaining case reported in detail elsewhere[1] the Staph. aureus was resistant to penicillin but sensitive to streptomycin, and the use of the latter drug resulted in recovery.

*Bacterial Endocarditis.* There were eight cases of acute bacterial endocarditis, in seven of which Staph. aureus was the causative organism and the tricuspid valve alone was the site of implantation. In the remaining case the aortic valve was involved and the responsible agent was the Pseudomonas aeruginosa (Bacillus pyocyaneus). The diagnosis of endocarditis of the right side of the heart was established clinically on the basis of a triad consisting of evidence of heroin addiction, septicemia including repeatedly positive blood cultures and x-ray evidence of pulmonary infarction in the absence of disease in the peripheral veins. Localization of the endocarditis to the tricuspid valve was inferred from the fact that there was no murmur indicative of pulmonic valve disease. Involvement of the pulmonic valve usually is manifested by the development of a murmur over this valve area. On the other hand, tricuspid valve endocarditis may often be present without a murmur or at best with a murmur that is anything but prominent.

Four of the eight patients died and were studied at autopsy, including the one with aortic valve disease due to Ps. aeruginosa. In this last case there were also septic infarcts in the spleen and kidneys. The autopsy examinations in the remaining three confirmed the clinical diagnosis of acute bacterial endocarditis of the tricuspid valve. There were many septic pulmonary infarcts showing all the gradations from slight necrosis to frank abscess. The vegetations were large and friable in all cases. There was no evidence of pre-existing valvular disease. Four patients recovered completely. The pulmonary infarcts in these cases were small, few in number and associated with little or no necrosis. They resolved satisfactorily with medical treatment only. The extent of pulmonary involvement was therefore in contrast to that observed in the fatal cases.

Three of the patients who recovered had additional complications. One of them developed signs of malaria late in the course of treatment of the endocarditis. Momentarily there was concern that the infection was not responding to penicillin. The doubt was resolved when plasmodia were discovered and specific therapy was instituted. Another had a small abscess on the forearm and purulent arthritis of the knee from which Staph. aureus was cultured. The third showed numerous abscesses on the hands.

All of the patients who recovered were treated with large doses of penicillin, administered over an eight-week period. The size of the dose was regulated in each instance according to the determined sensitivity of the staphylococcus and ranged from 200,000 to 2,000,000 units every two hours.

*Tetanus.* Tetanus was seen as a complication of drug addiction in seven cases and

was fatal in all but one. There was no other obvious portal of entry for the disease than the injection sites. In five of the patients, all heroin addicts, there were also multiple subcutaneous abscesses. In the remaining two who were morphine addicts there were no abscesses although there was a small area of cellulitis of the hand in one of them. One of the patients was of special interest. She was first admitted to the hospital in 1945 with multiple abscesses at the sites of injection of heroin, severe spasticity, generalized hyperactivity of the reflexes and inability to open the mouth. She was treated with sulfadiazine, penicillin, tetanus antitoxin and sedation, and recovered during sixty-three days of hospitalization. About sixteen months later she was readmitted with a similar picture; this time she succumbed. Apparently the reasons for a clinical diagnosis of tetanus were valid on both occasions although admittedly reinfection with tetanus is a rarity. Since this patient had two widely separated admissions, she enters the list twice.

*Malaria.* There were twenty-nine cases of malaria complicating heroin addiction. None of these patients gave a history of antecedent malaria and, in view of the rarity of the disease in Washington, it is unlikely that they represented naturally occurring malaria. The mode of infection appears to have been from person to person through the medium of the communal needle.

The cases were divided as follows: estivo-autumnal, fifteen cases; quartan, four cases and tertian, two cases. In the remaining eight patients plasmodia were found in the blood smears but the type was not identified.

Twenty-five of these patients had only malaria; four showed additional complications, namely, subcutaneous abscesses in three and tricuspid endocarditis in one. Treatment consisted of the administration of quinine, quinacrine, or both, and all patients recovered. The only other special treatment was incision and drainage of abscesses where indicated and penicillin therapy for the patient with endocarditis.

## COMMENTS

As was mentioned in the opening section of this article, the problem of infections attributable to narcotic addiction was related almost entirely to the use of heroin. The incidence of complications of morphine addiction was only 3 per cent as compared to 38 per cent for heroin. At first glance this difference might appear to be related entirely to some inherent contamination of the heroin. However, since a large number of white patients with heroin addiction were admitted to the hospital during the period of the study and yet only four had complications, it would seem that the heroin itself was not solely at fault. Rather, the factor of race was more important than the type of narcotic in explaining the development of complications. (Fig. 3.) All but six of the patients with complications were Negroes. This was not due to any susceptibility peculiar to the race; rather, it was probably related to the methods used for administering the drug. The omission of antisepsis and the use of a "community needle" obviously favored the occurrence of infections. In addition, however, the heroin itself must have played some part in the development of complications. It is otherwise difficult to explain the low incidence of infections in heroin addicts before 1943 and the marked increase which began in that year. The only exception to this statement is malaria which apparently was introduced after 1942 as a result of communal use of injection equipment. There is no reason to suppose that methods of administration of the drug differed in the two periods. We can conclude, therefore, that contamination of the heroin and technics of administration both contribute to the incidence of infections.

Recognition of addiction to heroin was important in the appraisal of the complicating infections. This applies less to the more obvious forms such as abscess and thrombophlebitis than to the occult infections such as malaria and endocarditis. We have come to the point of suspecting these

latter diseases whenever a heroin addict has fever. Ordinarily the stigmas of drug administration were obvious, taking the form of scars along the course of the superficial veins of the extremities as well as hardening and occlusion of most of these veins. Just as these stigmas at times led to the suspicion of certain complications, so occasionally the presence of the complications stimulated a more careful search for the stigmas. In this connection our experience emphasized that the patient's history often was unreliable because of the tendency to deny drug addiction even when there was obvious evidence to the contrary. Furthermore, it was always impossible to ascertain the amounts of heroin used. The drug is adulterated repeatedly in the transactions by those who sell it. The fact that withdrawal effects were rare, even in those patients who admitted daily use of supposedly large amounts, would seem to indicate that the quantities of pure heroin were really small.

Although skin abscesses were the most common type of infection developing in the heroin addicts of this study, we have been unable to discover direct reference to this topic in the literature. Probably the experience elsewhere corresponds to that at our own hospital where an occasional heroin addict with subcutaneous abscesses was seen and accepted as a matter of course hardly worth reporting. In all but one case in this series the abscesses appeared at sites of injection of the drug. Often they were multiple.

The systemic reaction in these cases was variable. Many of the patients had chiefly local discomfort from the abscesses. Even in the absence of bacteremia or other complication others appeared seriously ill; then there was septic fever, toxicity and leukocytosis. In general the prognosis in the patients with only abscesses was favorable. The presence of other complications was sometimes masked temporarily by the abscesses. This fact plus the knowledge that eighteen of the sixty-eight patients had such additional complications has impressed us with the necessity of searching routinely for evidence of bacterial endocarditis, thrombophlebitis and malaria particularly.

Acute thrombophlebitis is serious because it may be the suppurative variety and a potential source for septic pulmonary infarcts. Recognition of thrombophlebitis may depend on obvious signs of inflammation along the course of the vein, either superficial or deep, or on the demonstration of pulmonary infarction in a patient having an area of cellutitis or an abscess which is so extensive that the condition of the local veins cannot be evaluated. In addition to intensive therapy with penicillin it is our opinion that cases of this type should also have proximal venous ligation, as is generally recommended for suppurative thrombophlebitis.[2–6]

The fact that the seven patients with septicemia reported on herein recovered in spite of serious illnesses is a remarkable tribute to the effectiveness of penicillin. However, it should be emphasized that early diagnosis by means of blood cultures, determination of sensitivity of the causative organism to the antibiotic agents and administration of the agent selected in doses large enough to provide effective blood levels are mandatory.

All of the eight cases of bacterial endocarditis included in this study have been described in previous reports.[1,7,8] The only other references in the literature relating to this subject are concerned with monilemia with or without endocarditis.[9–12]

Our four patients who recovered all received large doses of penicillin over a period of 8 weeks.[8] In contrast the patients who died were seen at a time when penicillin was not plentiful or not available at all.[7] This clearly indicates the difference in prognosis which has resulted from the use of this agent.

An unusual feature of our cases of endocarditis was that the tricuspid valve was the only site of involvement in all but one case in which the aortic valve alone was affected. This is surprising in view of the fact that the tricuspid valve is involved by bacterial

endocarditis of any variety in about 3 per cent or less of cases.[13,14] There is no explanation for this discrepancy. The idea proposed by Wilhelm et al.[1] that the introduction of large numbers of bacteria directly into the veins favors their implantation on the tricuspid valve has no substantial support.

In contrast to endocarditis affecting other valves in which the development or modification of a murmur is almost invariable, none of our patients had a murmur which could be considered to be diagnostic of tricuspid valve disease.[15] This fact raises some question of the accuracy of the diagnosis in the patients who recovered. It might be supposed that the source for the pulmonary infarcts was in an obscure thrombophlebitis. There is no answer to this objection except to point out that there were no areas of abscess or cellulitis to obscure venous disease and that the fact of recovery was the only clinical difference from the fatal cases in which a diagnosis of tricuspid endocarditis was proved.

The last review of the subject of tetanus resulting from narcotic addiction was by Doane in 1924.[16] He added three cases to the total of nine previously reported by other authors. The mode of development and clinical course in our cases differed in no way from tetanus resulting from any contaminated puncture wound.

The literature concerning the development of malaria in narcotic addicts was reviewed by Schoenbach and Spingarn in 1942.[17] Most[18,19] has reported on 200 cases of this type in New York City alone. All reports emphasize that the disease is transmitted from person to person in a circle of addicts on account of the repeated use of the same injection equipment without antiseptic precautions. The development of malaria in this way is analogous to that which follows transfusion of blood containing plasmodia.[20,21]

Our twenty-nine cases of malaria appeared after 1943, indicating admission to the Washington circle of addicts of one or more individuals who were a reservoir for the disease. Until 1946 all cases were presumably of the falciparum type. In that year the appearance of one case of quartan malaria suggested that a new reservoir had been introduced. This was verified in 1947 when three additional cases of quartan malaria were observed and tertian malaria appeared for the first time. The course of the disease was mild in all cases and it responded readily to quinine or quinacrine or both. The benign nature of the disease is in strict contrast with experience in other localities where malaria in heroin addicts has been attended by a high mortality rate.[18,19] The presence of malaria in heroin addicts has an important public health aspect. Obviously these people are a potential source for transmission of malaria by mosquitoes to the general public although Wilner[22] has pointed out that the excellence of mosquito control in Washington makes this unlikely.

We have not included in this report any study of those narcotic addicts who suffered from infections which had no direct relation to their addiction. There were some addicts with diseases like pneumonia or acute pulmonary tuberculosis in whom it was difficult to decide this fact immediately, the tendency being to assume that the illness was related to the addiction.

## SUMMARY AND CONCLUSIONS*

1. Narcotic addiction presents an added problem because of the prevalence of complicating infections. The complications found in a group of 102 addicts included skin abscesses, thrombophlebitis, septicemia, bacterial endocarditis, tetanus and malaria.

2. Such complications are a result of the carelessness of narcotic addicts in administering the drug.

3. Early and adequate use of penicillin has had a remarkably beneficial effect on the prognosis and pathologic phenomena of

* Since this manuscript was submitted for publication, another report on bacterial endocarditis in narcotic addicts has been published. There were eleven cases with involvement of the aortic valve by streptococci predominating. (LUTTGENS, W. F. Endocarditis in "main line" opium addicts; report on eleven cases. *Arch. Int. Med.*, 83: 653, 1949.)

serious staphylococcic infections in these cases.

4. In febrile patients having the stigmas of drug addiction a careful search should be made for the complications enumerated herein.

*Acknowledgment.* We are indebted to Dr. Harry F. Dowling, Chief of the George Washington University Medical Division for permission to include cases studied in his Division.

REFERENCES

1. Wilhelm, Freda, Hirsh, H. L., Hussey, H. H. and Dowling, H. F. The treatment of acute bacterial endocarditis with penicillin. *Ann. Int. Med.*, 26: 221, 1947.
2. Ochsner, A. and DeBakey, M. Therapeutic considerations of thrombophlebitis and phlebothrombosis. *New England J. Med.*, 225: 207, 1941.
3. Collins, C. G., Jones, J. R. and Nelson, E. W. Surgical treatment of pelvic thrombophlebitis: ligation of inferior vena cava and ovarian veins: preliminary report. *New Orleans M. & S. J.*, 95: 324, 1943.
4. Hussey, H. H. and Katz, S. Septic pulmonary infarction; report of 8 cases. *Ann. Int. Med.*, 22: 526, 1945.
5. Veal, J. R. and Hussey, H. H. The surgical treatment of thrombosis of peripheral veins. *M. Ann. District of Columbia*, 12: 333, 1943.
6. Homans, J. Operative treatment of venous thrombosis in the lower limbs. *Am. J. Med.*, 3: 345, 1947.
7. Hussey, H. H., Keliher, T. F., Schaefer, B. F. and Walsh, B. J. Septicemia and bacterial endocarditis resulting from heroin addiction. *J. A. M. A.*, 126: 535, 1944.
8. Zeller, W. W., Hirsh, H. L., Dowling, H. F., Hussey, H. H. and Robinson, J. A. The treatment of bacterial endocarditis with penicillin and streptomycin. *M. Ann. District of Columbia*, 17: 21, 1948.
9. Joachim, H. and Polayes, S. H. Subacute endocarditis with systemic mycosis (Monilia). *J. A. M. A.*, 115: 205, 1940.
10. Polayes, S. H. and Emmons, C. W. Final report on identification of the organism of previously reported case of subacute endocarditis and systemic mycosis (Monilia). *J. A. M. A.*, 117: 1533, 1941.
11. Wikler, A., Williams, E. G., Douglass, E. D. and Emmons, C. W. Mycotic endocarditis. *J. A. M. A.*, 119: 333, 1942.
12. Wikler, A., Williams, E. G. and Wiesel, C. Monilemia associated with toxic purpura. *Arch. Neurol. & Psychiat.*, 50: 661, 1943.
13. Goldburgh, H. L., Baer, S. and Lieber, M. M. Acute bacterial endocarditis of the tricuspid valve. *Am. J. M. Sc.*, 204: 319, 1942.
14. Martin, W. B. and Spink, W. W. Endocarditis due to type B Hemophilus infleunzae involving only the tricuspid valve. *Am. J. M. Sc.*, 214: 139, 1947.
15. Hussey, H. H. The recognition of acute bacterial endocarditis. *Am. Practitioner*, 1: 409, 1947.
16. Doane, J. C. Tetanus as a complication in drug inebriety. *J. A. M. A.*, 82: 1105, 1924.
17. Schoenbach, E. B. and Spingarn, C. L. Inoculation malaria and drug addiction. *J. Mt. Sinai Hosp.*, 8: 998, 1942.
18. Most, H. Falciparum malaria among drug addicts: epidemiologic studies. *Am. J. Pub. Health*, 30: 403, 1940.
19. Most, H. Falciparum malaria in drug addicts: clinical aspects. *Am. J. Trop. Med.*, 20: 551, 1940.
20. Gordon, E. F. Accidental transmission of malaria. *J. A. M. A.*, 116: 1200, 1941.
21. Teasley, G. H. Malaria following blood transfusion. *Proc. Staff Meet., Mayo Clin.*, 21: 289, 1946.
22. Wilner, P. R. Clinical aspects of malaria. *M. Ann. District of Columbia*, 16: 469, 1947.

# Carcinoma of the Thyroid Gland*

## *A Clinical and Pathologic Study*

MORRIS E. DAILEY, M.D., MAYO H. SOLEY, M.D.† *and* STUART LINDSAY, M.D.
*San Francisco, California*

THE opinion that carcinomas of the thyroid occur infrequently is based primarily on data from autopsies. It has been reported recently that only five carcinomas of the thyroid were recorded in 18,668 autopsies at the Boston City Hospital.[1] In the Los Angeles General Hospital thirty-four instances of thyroid carcinomas have occurred among 36,500 postmortem examinations.[2] At the University of California Hospital in San Francisco four carcinomas of the thyroid were present in a recent series of 1,716 consecutive autopsies. On the other hand, in a series of 3,539 thyroidectomies of non-toxic glands encountered in our hospital 168 cases of carcinoma of the thyroid were present. Thus our own figures demonstrate approximately one carcinoma of the thyroid gland per 429 autopsies; yet, one was present in every twenty-one (4.8 per cent) surgical specimens. Frantz and her associates[3] found an incidence of carcinoma of 6.8 per cent in non-toxic goiter. This pronounced discrepancy between the incidence of carcinomas of the thyroid in surgical and postmortem specimens demands an explanation. We believe the pertinent points are: (1) Malignant nodular goiters which have been removed at surgery are often localized and a complete cure often is obtained, while those at autopsy are primarily far advanced malignancies. (2) The surgical material represents a selected group in that goiters displaying no clinical criteria of neoplasm are frequently not removed. (3) Patients with carcinoma of the thyroid, as a rule, do not die of this disease in the large teaching hospitals because terminal care is given in their home communities. This aspect of the problem has recently been emphasized by Anglem and Bradford.[4] It is evident that postmortem statistics from teaching hospitals in no way present the true picture regarding the frequency of malignancies of the thyroid.

Cancer of the thyroid gland invites attention because not only of its frequency but also, because of its location it may be diagnosed far earlier than many malignancies. Its tendency to occur in younger age groups is a persistent challenge to arrive at a prompt clinical suspicion of its presence. This form of malignancy is somewhat unique in that survival for long periods may occur even though local or distant metastases are present. The purpose of this report is to point out the incidence of the various types of carcinoma of the thyroid and to draw attention to certain features of the clinical examination which aid in arriving at an early diagnosis. This discussion is based on a study of ninety cases of carcinoma of the thyroid gland seen by the staff of the University of California Hospital between July, 1935, and May, 1947.

Clinically, the problem of carcinoma of the thyroid is concerned essentially with the differential diagnosis of non-toxic nodular goiter. Symmetrical malignancies involving most of the thyroid gland do occur but their frequency is low.

The duration of the goiter is important (Fig. 1) but it is notoriously difficult to make

* From the Divisions of Medicine and Pathology of the University of California School of Medicine, and the Thyroid Clinic of the University of California Hospital. Supported by the Donner Foundation, Cancer Research Division Philadelphia, Pa.

† Deceased.

the clinical inference that a given malignancy has arisen from a previously benign adenoma or involutionary nodule. This is true for three reasons: (1) Patients may be unaware of the presence of a goiter for many years and hence given an erroneously

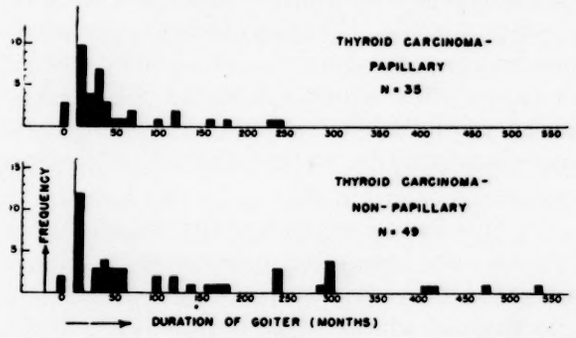



FIG. 1. Frequency of thyroid carcinoma in relation to duration of goiter. When the presence of goiter was unknown to the patient, its duration is recorded as zero.

brief history of its duration. (2) Certain malignancies grow so slowly as to lead to the conclusion that a nodular goiter had harbored malignancy for several years. (3) A malignancy may arise in areas of the thyroid totally independent of long-recognized nodules.

The sex of a patient is important because a nodular goiter is more likely to be malignant in a man than in a woman. Ward's data[5] indicate that non-toxic nodular goiters will be malignant in one of seventeen males while the ratio is 1 in 44 among females. Of the patients in the present series seventy-nine were females and eleven were males. The age of the patient is noteworthy. (Fig. 2.) Under the age of twenty, nodular goiter due solely to involutionary changes is relatively uncommon. In a recent series of seventy-two involutionary goiters[6] none occurred under the age of twenty, yet nearly 20 per cent of our patients with carcinoma were under this age at the time of the goiter's appearance. Rapidly increasing local pressure symptoms suggest a growing tumor. A history of growth of a nodule merits attention but this is more significant if rapid and recent and associated with the concurrent appearance of pressure symptoms.

A most significant point on physical examination is the discovery of a solitary nodule for, as has been shown, 11 to 24 per cent of such nodules will be malignant, regardless of all other factors.[7,8] The consistency of a nodule does not aid greatly in

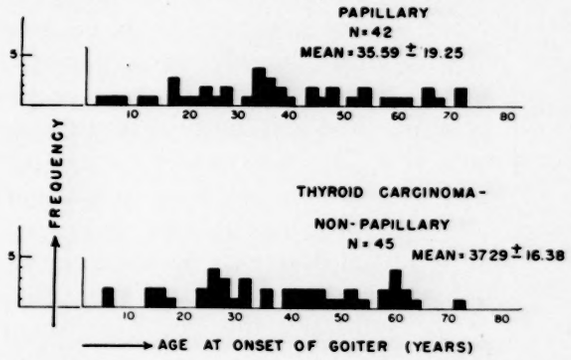



FIG. 2. Frequency of thyroid carcinoma in relation to age of patient.

making the diagnosis of malignancy because many tumors have a soft, meaty consistency and, conversely, many involutionary nodules, due to degenerative and calcific changes, are hard. Objective evidence of vocal cord paralysis is suggestive of malignancy but hoarseness is not. Paralysis is most frequently due to actual invasion and

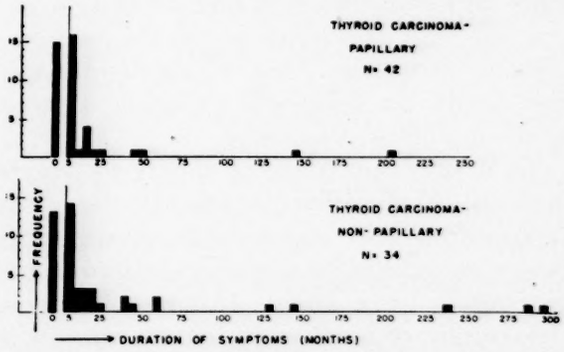



FIG. 3. Local pressure symptoms in general of brief duration; a sizable proportion of the patients complained of no pressure effects.

pressure on the recurrent laryngeal nerve while hoarseness *per se* may be due to tracheal pressure and displacement caused by any type of goiter. Thirty-two per cent of our patients with involutionary goiters and 30 per cent with carcinomas had hoarseness as a symptom but only 11 per cent of those who were hoarse in the former

group had vocal cord paralysis. Seventy-six per cent with hoarseness associated with malignancy had paralysis of the vocal cords.

The presence or absence of a family history of goiter or of residence in an endemic goiter area has not proved helpful in establishing a diagnosis of carcinoma of the thyroid. Quite possibly this is because our patients come largely from endemic areas and so final appraisal of these points is not possible. The specific type of pressure symptoms (Fig. 3) in order of occurrence are: local pressure, hoarseness, dysphagia, cough and excessive mucus, and do not aid in the differential diagnosis between malignant and non-malignant goiters since they occur with essentially the same frequency in both groups.

### PATHOLOGIC CLASSIFICATION

The surgical and gross pathologic descriptions, and slides and blocks of the thyroid tissues, were available for study. The neoplasms were placed in three main groups according to their gross and microscopic characteristics. Warren's[8] classification of thyroid neoplasms was used with certain modification; the presence or absence of metastases was disregarded in the grading and classification of the primary thyroid neoplasm. Our classification was first made on histologic grounds without reviewing clinical histories.

In a previous study of ninety-six single nodules of the thyroid gland[7] the close relationship and apparent progression between adenomas, malignant adenomas and carcinoma were noted. In some instances the origin of a thyroid carcinoma in a previously benign neoplasm or adenoma could be determined from the clinical history and the microscopic character of the tumor, its capsule and its extent of growth. Frequently gross or microscopic evidence of a possible benign origin of the lesion had been obscured and destroyed by invasive malignant tissue.

A secondary epithelial proliferative reaction is common in involutionary nodules; the possibility that this proliferation might become neoplastic and even malignant has been suggested. In the group of carcinomas herein reported there were two malignant invasive neoplasms which showed definite histologic evidence that the malignant process had originated in the secondary epithelial proliferation within an involutionary nodule. Certainly the proliferating but benign tissue in an involutionary nodule or in a nodule which cannot be classified as to an involutionary or neoplastic origin is indistinguishable from that of a benign neoplasm or adenoma.

In this group of malignant thyroid neoplasms only invasive tumors were included. In a group of ninety-six single nodules of the thyroid gland studied previously there were two tumors which showed histologic cellular evidence of malignancy without demonstrable transcapsular or vascular invasion. These were classified as malignant adenomas. One additional nodule in that group was locally invasive; but because the tumor otherwise appeared histologically benign, it was classified as an invasive adenoma.

Those nodules which are circumscribed or encapsulated, but which show capsular and vascular invasion, have been classified by Warren as adenomas with invasion. Since these tumors, with only one exception in our experience, show additional cellular evidence of malignancy, we have preferred to classify them as carcinomas. Aside from evidence of invasion the histologic line of distinction between a benign and a histologically malignant but non-invasive adenoma is in some instances difficult to draw. A detailed pathologic study of thyroid neoplasms will be reported later.

### CLASSIFICATION OF NINETY CARCINOMAS OF THE THYROID GLAND

*Group I.* These neoplasms are circumscribed, often encapsulated, and may show minimal or gross evidence of capsular or vascular invasion. In most instances local neoplastic invasion was demonstrable but had not extended widely from the primary

focus. The gross appearance of the neoplastic tissue depends upon the pattern of the growing tissue. The cut surface of the neoplasm usually has a homogeneous pinkish-tan color with an opaque appearance. With greater degrees of differentiation of the tumor and with the appearance of colloid in the neoplastic acini, the surface of the tumor is more moist, pink and translucent. The papillary neoplasms are characterized by granular, opaque, dry, pale tissue, often with cystic degeneration.

Microscopically, the tumors in group I show a fairly high degree of differentiation, but with greater degrees of cellular pleomorphism, hyperchromatism and more numerous mitoses than the corresponding adenoma or involutionary nodule. The pattern may be embryonal with the formation of solid sheets of cells, or glandular with formation of acini of varying size, with or without colloid. Papillary and Hürthle cell tumors may be present in this group. These various patterns correspond to the benign counterparts but show low-grade malignant cellular characteristics in addition to invasion. Neoplasms in group I are of the lowest grade of malignancy; there were eighteen cases in this group.

*Group II.* In group II the neoplasms generally are larger and extend more widely within the thyroid gland and through its capsule. The cut surface is generally less uniform and homogeneous than the less malignant tumors. Hemorrhage, necrosis and gross evidence of vascular invasion are more common. Microscopically, these neoplasms show increasing histologic evidence of rapid growth. Mitoses are more numerous and nuclear chromatin is abundant in most instances. In the papillary tumors in this group the neoplastic cells covering the papillary processes ordinarily show considerable stratification. A glandular type of neoplastic structure often forms much of the fundamentally papillary tumor. Hürthle cell tumors also occur in this group. The neoplasms in group II are of moderate malignancy; there were sixty-two cases in this group.

*Group III.* (10 Cases) This group includes those neoplasms of the thyroid gland with the highest degree of malignancy. They are usually large, bulky, rapidly growing neoplasms, often demonstrating extensive intraglandular and extraglandular invasion. The neoplastic growth is frequently accompanied by degeneration, necrosis and hemorrhage within the tumor. Extension through the skin of the neck and grossly evident venous invasion may be noted. Anaplasia is often extreme and multinucleated cells and mitotic figures are abundant. A tendency to formation of glandular and papillary structures, or the formation and storage of colloid, is not a prominent feature of these dedifferentiated neoplasms. There were ten cases in group III.

## COMMENTS

Certain conclusions can be reached regarding the fate of the patients in our series even though the length of follow-up in the more recent cases is short. The period of survival after surgery is not significantly different in our groups I and II (49.3 months and 38.4 months, respectively). However, of the ten cases in group III six were dead in an average period of 14.2 months postoperatively. This is a statistically significant difference from the survival periods in groups I and II. Surprisingly, these patients with papillary tumors had the same survival period (probably due to our short follow-up in recent cases) as those with non-papillary tumors.

Nine patients warrant special mention in that they are alive an average of 6.9 years (range three to seventeen years) after the demonstration of distant metastases. (Table I.) This toleration of remote metastases is not unique for malignancy of the thyroid but its clinical importance is obvious.

A total of twenty-three deaths occurred in our group of ninety cases. The leading cause of death was respiratory obstruction (eleven cases); eight died of multiple remote metastases, two postoperatively and two of other diseases, but they were known still to possess unremoved neoplastic tissue.

Treatment of early cancer of the thyroid is radical resection of the involved lobe and isthmus when the disease is clearly unilateral. In larger tumors total thyroidectomy is accomplished together with removal of involved adjacent tissue. In all instances

TABLE I

| Age at Time of Discovery of Metastases | Sex | Type of Primary Tumor | Site of Metastases | Years Survival after Metastatic Spread |
|---|---|---|---|---|
| 8 | M | Papillary carcinoma | Lungs | 17 |
| 52 | F | Papillary adenocarcinoma | Breast and sternum | 3 |
| 57 | F | Adenocarcinoma | Skull | 8* |
| 45 | F | Adenocarcinoma | Sacrum | 10* |
| 50 | F | Malignant adenoma | Femur | 3 |
| 43 | F | Papillary carcinoma | Sternum | 7 |
| 60 | F | Adenocarcinoma | Orbit | 5* |
| 59 | M | Adenocarcinoma | Skull | 5* |
| 65 | F | Adenocarcinoma | Sternum | 4 |

* Dead.

in which a possibility of metastatic spread to the cervical nodes is suspected at surgery, radical neck dissection is carried out. Palliative surgery, quite frequently with tracheotomy, is often all that can be done when one is confronted with an extensive, rapidly growing, anaplastic tumor (group III). It seems reasonable to make as thorough an attack on the primary tumor as possible even though distant metastases are present, since these remote implants may be tolerated for many years. Emphasis again should be placed on the need for radical removal of all solitary nodules in the thyroid because of the high incidence of benign and malignant tumors in that organ.

Radiation therapy is used in the inoperable tumors, not with the expectancy of obtaining a cure but rather to relieve specific pressure symptoms. This form of therapy, in our hands, has been distinctly disappointing. Indeed, re-operation is preferred, especially in the papillary group, rather than subjection of all patients to routine postoperative radiation.

Radioactive iodine offers limited but definite possibilities of therapeutic usefulness. In patients with malignancies of the thyroid, expected to be inoperable, a test dose (usually 2.0 millicuries $I^{131}$) of radioactive iodine is administered orally and twenty-four to forty-eight hours later, a portion of the tumor is obtained at surgery. By radio-autography and microscopic study it is then determined whether the radioactive iodine has been taken up in the tumor tissue proper. If the iodine has been localized in the tumor, a larger therapeutic dose may be given.

From our work and that of others it appears that very few carcinomas of the thyroid will take up an adequate amount of radioactive iodine to make this form of treatment of value therapeutically. An increase in uptake may occur in the metastases after total thyroidectomy or following the administration of thyrotropic hormone as suggested by Seidlin.[9]

We have attempted therapy with radioactive iodine in three patients with carcinoma of the thyroid. The largest dose given at a single time was 100 millicuries. Myxedema will develop in two to three months in patients receiving therapy. Signs of thyroid toxicity may occur initially due to the disintegration of a thyroid carcinoma which elaborates hormone. No proof of cure is known to us and alteration in size of visceral metastases is difficult to evaluate, although Salter[10] has demonstrated that radioiodine produced a diminution in size of the pulmonary and hilar infiltrations due to metastases from a thyroid carcinoma.

## SUMMARY

A series of ninety patients with carcinoma of the thyroid was studied from the pathologic and clinical standpoint. Postoperative survival is distinctly less in the anaplastic carcinomas. Salient clinical features suggestive of malignancy include a nodular goiter under the age of twenty, recent

growth, vocal cord paralysis and the presence of a single nodule. Radical thyroidectomy is the preferable treatment, with roentgen therapy or radioactive iodine being reserved in general for inoperable recurrences or metastases.

REFERENCES


1. Vanderlaan, W. P. The occurrence of carcinoma of the thyroid gland in autopsy material. *New England J. Med.*, 237: 221–222, 1947.
2. Steiner, P. E. Personal communication.
3. Frantz, V. K., Quimby, E. and Evans, T. C. Radioactive iodine studies of functional thyroid carcinoma. *Radiology*, 51: 532–552, 1948.
4. Anglem, T. J. and Bradford, M. L. Nodular goiter and thyroid cancer. *New England J. Med.*, 239: 217–220, 1948.
5. Ward, R. Malignant goiter. *Surgery*, 16: 783–803, 1944.
6. Dailey, M. E., Soley, M. H. and Lindsay, S. The clinical differentiation of various types of nontoxic nodular goiter. *Arch. Int. Med.*, 83: 382–389, 1949.
7. Soley, M. H., Lindsay, S. and Dailey, M. E. The clinical significance of a solitary nodule in the thyroid gland. *West. J. Surg.*, 56: 96–104, 1948.
8. Cole, W. H., Slaughter, D. P. and Rossiter, L. J. Potential dangers of non-toxic nodular goiters. *J. A. M. A.*, 127: 883–888, 1945.
9. Warren, S. The classification of tumors of the thyroid. *Am. J. Roentgenol.*, 46: 447–450, 1941.
10. Seidlin, S. M., Oshry, E. and Yalow, A. A. Twelve cases of metastatic carcinoma of the thyroid studied with radioiodine. Proc. A. for the Study of Internal Secretion, June, 1947.
11. Salter, W. T., Johnston, M. and Gemmel, J. Turnover rates as measured by radioiodine. Brookhaven Conference Report, pp. 24–33. Assoc. Universities, Inc., Upton, N. Y., 1948.

# Reviews

## The Present Status of Potassium Therapy*

J. R. ELKINTON, M.D. *and* R. TARAIL, M.D.
*Philadelphia, Pennsylvania*

THE administration of potassium has recently been recognized to be of benefit in a variety of clinical disorders.[1–5] The diagnosis and treatment of deficiencies of this predominantly intracellular component of body fluids are attended with greater difficulties than are those of the extracellular electrolytes, sodium, chloride and bicarbonate. The purpose of this paper is to discuss certain of the practical aspects and dangers of the administration of potassium and to define its present status as a therapeutic procedure.

### CIRCUMSTANCES WHICH MAY RESULT IN POTASSIUM DEFICIENCY

*Obligatory excretion* of potassium in excess of intake, if sufficiently protracted in time, leads to deficiency of the ion. In many clinical situations in which the intake of potassium is restricted because of inability to eat, a negative balance of potassium ensues as a result of its continued excretion in the *urine.*[2] Such urinary excretion may be accelerated by dehydration[6–8] and trauma to tissue.[4,9] The negative balance due to renal losses of potassium may be further augmented by loss of potassium in abnormal drainages of *gastrointestinal fluids.*[2,4,10–12] It is not surprising, therefore, that potassium deficits are found in clinical conditions such as postoperative states and gastrointestinal disturbances, in which large amounts of fluid are lost by vomiting, gastrointestinal suction, drainage from fistulas, diarrhea or steatorrhea. It is in precisely such patients, maintained on the usual potassium-free parenteral fluids, that the intake of potassium is restricted, its excretion continues and a deficiency develops.

Administration or overproduction of some of the steroids of the adrenal cortex may accelerate the renal excretion of potassium and, in the absence of adequate intake, lead to a deficiency of the ion. This phenomenon has been observed in patients with Addison's disease who have been given large doses of desoxycorticosterone[13] or adrenocortical extract[14] and in other patients treated with ACTH[15,16] and with cortisone.[17,18] In some cases of Cushing's syndrome hyperactivity of the adrenal cortex appears to be associated with potassium deficiency.[19]

*Movements of potassium into and out of cells* in relation to cellular metabolism may add to the abnormalities of potassium distribution resulting from uncompensated loss of the ion through the kidneys. This is true in diabetic acidosis.[20] As the condition develops, the accelerated renal excretion of potassium and extrarenal losses fail to keep pace with the increased rate of release of the ion from the cells of the body and with contraction of extracellular volume. Serum potassium is usually, therefore, either elevated or normal before treatment is begun. After therapy is started, potassium excretion decreases, extracellular volume expands, and the rate of liberation of potassium from the cells declines sharply.[20] This leads to a precipitous fall in the concentration of serum potassium within four to twenty-four hours. The importance of cellular exchanges in producing diminution of the concentration of serum potassium can also be inferred in other disturbances of hydration,[2,21] in

* From the Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pa., and the Department of Biochemistry, Boston University School of Medicine, Boston, Mass.

familial periodic paralysis[22,23] and in certain subjects receiving insulin,[24] testosterone[25] and glucose.[26]

*Other disturbances of the internal equilibrium of electrolytes* may also be a factor in the development of cellular deficit of potassium. Darrow and his co-workers[27] have advanced experimental evidence of interdependence of deficit of cellular potassium, transfers of cellular sodium and alkalosis. They pointed out that in the presence of adequate renal function, the development of alkalosis leads to transfer of sodium from the extracellular to the intracellular fluids with a displacement of potassium from the latter. In clinical states of alkalosis or bicarbonate excess due to chloride deficit (or in pyloric obstruction or congenital malabsorption of chloride) such a mechanism may be operative; in such cases, however, the deficit of potassium probably is due primarily to the oligatory excretion of potassium in the absence of intake of the ion[2] rather than to the alkalosis *per se*. Treatment with solutions of chloride and sodium alone will not correct the alkalosis; not until the deficit of potassium has been corrected does the serum bicarbonate return to normal level.

## CLINICAL SIGNIFICANCE OF POTASSIUM DEFICIENCY

It is difficult to establish the exact disorders of function which result from deficiency of potassium. Quantitatively the intracellular phase of tissues contributes the major portion of the lost potassium but usually the extracellular fluids are relatively, if not absolutely, depleted of the ion as well (i.e., the concentration of potassium is lowered). Flaccid paralysis has been shown to be associated with the latter in the specific disease, familial periodic paralysis.[28] There have been occasional case reports in other conditions of sudden flaccid paralysis and of respiratory embarrassment which were similar to the sequence of events in familial periodic paralysis in onset, in association with hypokaliemia and in rapid response to potassium treatment. But comparable reduction of serum potassium and, presumably analogous, cellular deficits have been observed more frequently without severe neuromuscular signs or symptoms or, at the most, with diminished deep reflexes.[2,5] In such a heterogeneous group of severe illnesses it is difficult to determine whether or not muscular weakness or respiratory embarrassment are specifically related to alteration in potassium metabolism.

Electrocardiographic abnormalities occur regularly when the serum potassium concentration is low[29–31] The abnormalities include depressed, broadened T waves, prolonged Q-T interval and depression of the S-T segment. These electrocardiographic changes are not specific since some or all of them may occur in the course of other cardiac disturbances. But when associated with abnormal potassium transfers, such electrocardiographic changes appear to depend on alterations in the concentration of potassium in extracellular fluid rather than on changes in cellular content of the ion.[32]

The evidence to date is inconclusive in respect to the specific benefit of potassium therapy to cellular function (whether skeletal muscle, cardiac muscle or other tissues). The rationale of such treatment, therefore, depends principally on the ground that it is desirable to replace a substance in which the body is deficient. Potassium, like protein, is an essential constituent of the cells of the body, and replacement and prevention of loss of potassium is as logical as similar procedures in the case of protein. Proof of this is difficult to obtain in clinical conditions with highly unpredictable prognoses. In one condition with a more predictable course, diarrhea of infants, the case fatality rate in one series appeared to be definitely lowered by the administration of potassium.[33]

## RECOGNITION OF POTASSIUM DEFICIENCY

Since specific symptoms or signs are exceptional and if present may be indistinguishable from those of potassium intoxication, the diagnosis of potassium deficiency depends to a large extent on

recognition of the conditions which lead to its development. These conditions consist primarily of inadequate intake of potassium, usually over a prolonged period, during which renal and extrarenal excretion of the ion are unchecked or accelerated. As most foods contain considerable quantities of potassium, an ordinary diet contains adequate quantities of the ion. The range of intake of potassium in normal diets is 42 mEq. to 135 mEq. per day. But a patient sustained on parenteral fluids is on an intake low in potassium because these fluids, including those high in nitrogen content, as a rule contain practically no potassium.

The determination of the serum potassium concentration is the most useful chemical aid in the evaluation of potassium deficiency. This determination gives an indication of the state of extracellular potassium but does not necessarily reflect the state of cellular stores of the ion. Usually significant deficits of cellular potassium are associated with lowered concentration of extracellular and serum potassium (below 3.5 mEq./L.). In some cases, however, the extracellular concentration may be within the normal range (3.5 to 5.3 mEq./L.). In still other cases (commonly those characterized by severe dehydration such as in diabetic coma and infant diarrhea), the initial concentration of potassium before fluid therapy may actually be elevated despite the cellular depletion of the ion.[2,3,20,34] This paradox may be related to peripheral vascular collapse, contraction of extracellular volume, oliguria on one hand and, on the other, to an extremely high rate of cellular release of potassium. Thus an abnormally low concentration of potassium in serum is strongly suggestive of a cellular deficit of potassium but a normal or elevated concentration of serum potassium does not necessarily exclude such a deficit.

In the absence of laboratory facilities for the chemical determination of potassium in serum, changes in the electrocardiogram provide supplementary data only insofar as such changes are due to alteration in the level of serum potassium.

Elevation of the concentration of serum bicarbonate or $CO_2$ content is often the first chemical indication of the presence of a potassium deficiency. This is true only if the high $CO_2$ content is due to a metabolic alkalosis; primary respiratory retention of $CO_2$ with acidosis is fairly well ruled out by a normal or high blood pH and the absence of signs of pulmonary disease. If, at the same time, the serum level of potassium is depressed, a cellular deficit of potassium can be assumed and the response to therapy predicted. Uptake of potassium by the cells usually will be accompanied by release of cellular sodium and a return of the serum bicarbonate level to normal.[5]

One other chemical procedure is diagnostic at least in retrospect. Since potassium given to normal subjects is not retained to any great extent over a twenty-four-hour period, retention by a patient of administered potassium is probably good evidence of a pre-existing deficit of the ion.[2] This requires the measurement of the potassium balance (total intake − total output) which is usually a research procedure. Only by measuring the cumulative balance until potassium given is no longer retained can the total deficit be quantitated. This statement must be qualified by the possibilities that cellular retention of administered potassium beyond the existing deficit may be produced in diseased subjects, and that unmeasured losses of the ion via the skin may magnify the extent of positive balances. A small negative balance may be measured *before* potassium is given; such a finding indicates only a possible mode of occurrence but not the extent of depletion of the ion which has already taken place.

## CORRECTION OF POTASSIUM DEFICIENCY

*Dosage* of potassium is empirical and the doses suggested here are the estimates based on our own experience and on the reports of others.[1–3,5,12] The magnitude of cellular deficits of potassium, as measured by retention of the ion during treatment, may vary widely. The ranges of these deficits in mEq./kg. of body weight in various condi-

tions have been reported as follows: in diabetic acidosis, 2.4 to 7.9; in gastrointestinal cases on low potassium intake, 3.8 to 15.6; in infant diarrhea, 5.8 to 17.3. The higher values may be due in part to losses of potassium through the skin and to retention of potassium in excess of the prior deficit. In a 60 kg. adult in the first two of these categories this range represents a cellular deficit of potassium of 228 to 936 mEq. A daily dose of 75 to 150 mEq., prescribed according to the severity of the disease, should replace the deficit in three to twelve days. Some of this potassium, of course, will be excreted during therapy. The daily dose required to maintain a patient in potassium balance is estimated in the light of the following facts: (1) the quantity of potassium in an ordinary daily diet ranges from 42 to 135 mEq. with an average of about 90 mEq.,[35] and (2) the minimal daily excretion of potassium by subjects who are not receiving the ion, is 1 to 90 mEq.[2] The normal daily requirement of potassium for maintenance, therefore, is estimated to be 50 to 100 mEq. equivalents.

*Route* of administration of potassium may be oral or parenteral. Patients who can take potassium *by mouth* without distress are usually well enough to take liquid or solid foods containing adequate quantities of the ion. However, supplementary amounts of the ion may be given orally in such liquids as milk, ginger ale or orange juice in concentration of *added potassium* of 80 to 120 mEq./L. The oral route is used to advantage to administer potassium salts to patients with familial periodic paralysis or with other disturbances in which impairment of appetite is slight but who require potassium for long periods in quantities greater than can be provided conveniently from natural sources.

Potassium salts, however disguised, may be poorly tolerated when taken orally by patients with anorexia or nausea. In such subjects, and in patients maintained entirely by parenteral fluids, potassium can be given by the *intravenous* or *subcutaneous* route in quantities sufficient to prevent or to correct deficit. The administration of potassium by parenteral routes is safe provided the contraindications listed below are heeded and provided certain precautions are taken. These precautions include the avoidance of solutions with concentrations of potassium over 70 to 80 mEq./L. and rates of infusions above 20 mEq. per hour. Administration of solutions with higher concentrations and at faster rates without untoward results have been reported.[12] But the authors believe that the precautions defined above are advisable in general clinical practice.

*The solution for parenteral administration* may be prepared with a number of different salts of potassium. Potassium chloride is the easiest salt to use since its addition to other solutions produces no significant change in pH. One gm. of potassium chloride contains 13.4 mEq. of potassium; 6 gm. of potassium chloride added to 1 L. of solution therefore results in a concentration of 81 mEq. of potassium per L. The phosphate salts are the more logical form since the phosphate is an intracellular anion, a deficiency of which may exist along with that of potassium, especially in diabetic acidosis.[36] One difficulty in using phosphate lies in the fact that the dibasic phosphate, $K_2HPO_4$, and the monobasic phosphate, $KH_2PO_4$, must be combined in a molar ratio of 3.55 to 1.0 (ratio by weight of 4.5 to 1.0) to yield a pH of 7.35. When added to 1 L. of solution, 4.5 gm. of $K_2HPO_4$ (1 gm. contains 11.5 mEq. of potassium) and 1.0 gm. of $KH_2PO_4$ (contains 7.3 mEq. of potassium) yield a concentration of 60 mEq. of potassium per L. A given dose of potassium in the form of either one of these salts can be dissolved in a small volume of distilled water, boiled, and added to any of the usual parenteral fluids (glucose, physiologic saline or protein hydrolysate), other than blood or its substitutes.

The transfer of potassium into cells is accompanied by water in amounts determined by the increment of osmotic pressure of cellular solutes. For this reason isotonic solutions of extracellular plus intracellular electrolytes have been proposed for use instead of simply adding potassium salts to

solutions of extracellular electrolytes already isotonic with the body fluids. The best known of these solutions in pediatric practice are those of Darrow[1] and of Butler.[37] Darrow's solution is composed of KCl, $NaHCO_3$ and NaCl; Butler substitutes $K_2HPO_4$ for some of the KCl in the same combination (Table I, A and B). The concentration of K in these solutions is 35 and 20 mEq./L., respectively.

The authors believe that it is frequently desirable to treat adults deficient in potassium with somewhat stronger solutions of the ion, and have used solutions containing 60 to 80 mEq./L.[2,5] This concentration is probably safer than the higher one of 154 mEq./L. of K used by Bellet et al.[12,34] yet contains enough potassium to be therapeutically effective. Such solutions of $K_2HPO_4$ plus $KH_2PO_4$ and of KCl, made up to isotonicity with NaCl, are shown in Table I, D and E. In patients with potassium deficiency and alkalosis, who require more chloride than sodium because of the excess of cellular sodium, one of the authors (J. R. E.) has found a combination of $K_2HPO_4$, $KH_2PO_4$, KCl and NaCl to be therapeutically successful. (Table I, C.[5]) This solution provides an excess of Cl to combine with the displaced cellular Na, and $HPO_4^=$ as an anion to enter cells with the cation, potassium. Glucose probably should be administered with potassium-containing solutions since acceleration of carbohydrate combustion in peripheral tissues and deposition of glycogen have both been shown to facilitate the transfer of potassium into cells.[38] Glucose in concentrated form may be added to the solutions to make a final concentration of 50 gm. per L., or may be given separately as 10 per cent glucose solution. In patients deprived of food for any prolonged period it is desirable to administer protein hydrolysate to maintain the nitrogen equilibrium or protein stores of the body. Since potassium is usually lost in excess of the normal ratio of potassium to nitrogen (2.4–3.0 mEq. to 1.0 gm.), it is reasonable to supply about 5 mEq. of K to 1 gm. of N. Thus 1 L. of any of the solutions containing K in concentration of 70 to 80 mEq./L. would supply K in excess of the 12.4 gm. N contained in 2 L. of 5 per cent casein hydrolysate (amigen®).

*Control of therapy* must be exercised primarily by serial determinations of the serum potassium level. This is facilitated by the use of a reliable flame photometer. As indicated previously, cellular deficits of potassium may not always be accompanied by an abnormally low concentration in serum but a low serum concentration usually is associated with a cellular deficit. In diabetic coma and other states of severe dehydration extensive cellular deficit is frequently masked by an initial hyperkaliemia. If and when an abrupt fall in serum concentration has occurred following the use of non-potassium-containing solutions (usually within

TABLE I
SOLUTIONS FOR THE PARENTERAL ADMINISTRATION OF POTASSIUM

| Solution and Indication | Salt | Concentration of Salt | Concentration of Ions | | | |
|---|---|---|---|---|---|---|
| | | | Cl | Na | K | Na + K |
| | | (gm./L. | (mEq./L.) | | | |
| A. For infant diarrhea with acidosis (Darrow[1]) | KCl | 2.7 | 35 | ... | 35 | ... |
| | NaCl | 4.0 | 69 | 69 | .. | ... |
| | $NaHCO_3$ | 4.4 | ... | 53 | .. | ... |
| | ..... | ... | 104 | 122 | 35 | 157 |
| B. For infant diarrhea with acidosis* (Butler[37]) | KCl | 0.9 | 12 | ... | 12 | ... |
| | $K_2HPO_4$ | 0.3 | ... | ... | 3 | ... |
| | NaCl | 0.6 | 10 | 10 | .. | ... |
| | Na lactate | 2.2 | ... | 20 | .. | ... |
| | ..... | ... | 22 | 30 | 15 | 45 |
| C. For K deficiency with alkalosis†[5] | $K_2HPO_4$ | 3.2 | ... | ... | 37 | ... |
| | $KH_2PO_4$ | 0.7 | ... | ... | 5 | ... |
| | KCl | 3.0 | 40 | ... | 40 | ... |
| | NaCl | 4.2 | 72 | 72 | .. | ... |
| | ..... | ... | 112 | 72 | 82 | 154 |
| D. For K deficiency[2] ... | $K_2HPO_4$ | 4.5 | ... | ... | 53 | ... |
| | $KH_2PO_4$ | 1.0 | ... | ... | 7 | ... |
| | NaCl | 5.5 | 94 | 94 | .. | ... |
| | ..... | ... | 94 | 94 | 60 | 154 |
| E. For K deficiency[5] ... | KCl | 6.0 | 81 | ... | 81 | ... |
| | NaCl | 4.3 | 73 | 73 | .. | ... |
| | ..... | ... | 154 | 73 | 81 | 154 |

* Make up in 10 per cent glucose solution.
† Make salts up in 900 ml. distilled water and autoclave; then add 100 ml. of 50 per cent glucose to make 1 L.

eight hours of the beginning of treatment), the full sized doses of potassium recommended for severe cellular deficit may be given (75 to 150 mEq. per day). In the authors' opinion it is unwise to attempt to correct cellular deficits of potassium while the serum level of potassium is high-normal or elevated, because the dangers appear to outweigh the benefits.

Potassium therapy is indicated as long as the serum concentration remains below 3.5 mEq./L. Restoration of the serum concentration to and maintenance at normal levels is probably the simplest indication of adequate treatment. In the absence of facilities for the determination of the concentration of potassium in serum, electrocardiographic studies are of aid, particularly when cardiotoxic effects of elevation of serum potassium can be demonstrated.[30]

### DANGERS OF POTASSIUM TREATMENT AND ITS CONTRAINDICATIONS

The great danger of potassium therapy is the production of cardiac arrest by abnormal elevation of the concentration of potassium in serum and extracellular fluid. Elevation and pointing of the T wave and impaired intraventricular conduction resulting from elevation of the concentration of serum potassium have been produced in the dog at concentrations of 5.0 to 7.8 mEq./L. and at 9.4 to 12.0 mEq./L., respectively.[39] In patients, however,[30] the evidence indicates that serious conduction disturbances may occur at concentrations above 7.0 mEq./L. and that there may be considerable elevation and peaking of the T wave at concentrations above 6.5 mEq./L. A similar critical level has been found for the dog heart-lung preparation.[40] A serum potassium concentration in excess of 5.3 mEq./L. (upper limit of normal) or an electrocardiogram suggestive of elevated serum potassium are, therefore, definite contraindications to potassium therapy. The hazard of administering potassium to correct or prevent a deficit is increased if the serum potassium level is not known before potassium is given. This does not parallel exactly the situation with respect to replacement of extracellular electrolytes, chloride and sodium, which can be more safely initiated without prior knowledge of their concentrations in serum. A similar policy with respect to potassium may lead to toxic effects since the serum concentration may be high despite cellular depletion of the ion.

The normal subject rapidly excretes administered potassium through the kidneys, and the patient with a cellular deficit of the ion transfers such potassium from the extracellular space to the cells.[41] Patients with renal insufficiency, with or without cellular deficits of potassium, may excrete potassium poorly and readily develop an elevated concentration in serum.[41–43] This is especially true if the patient is oliguric or anuric. The patient with renal insufficiency and oliguria or anuria, therefore, should be given potassium either with extreme caution or not at all. In certain patients with renal disease the serum potassium concentration is low.[43] Small quantities may be given to maintain the serum potassium at the lower limit of the normal range. But in general it is advisable to withhold potassium therapy if oliguria is present.

Treatment with potassium may be dangerous if the serum concentration of calcium is low. Concurrent use of calcium may prevent the occurrence of tetany.[44]

### SUMMARY

Potassium deficiency is related to an obligatory and persistent excretion of potassium in the absence of intake of the ion, and under certain circumstances to the presence of bicarbonate excess or alkalosis. Such deficiency is found in starvation, dehydration, gastrointestinal disturbances and diabetic acidosis, and may be induced in Addison's disease by overtreatment with desoxycorticosterone, and in other conditions by the administration of ACTH or cortisone.

Specific signs and symptoms are usually not present. The diagnosis depends on recognition of etiologic circumstances and is

aided by the finding of abnormally low concentrations of potassium in serum. The diagnosis is most readily proven by the retention of the administered ion.

Dosage of administered potassium may range in the adult from 30 to 150 mEq. per day, the amount and duration of therapy being determined empirically. Chloride or phosphate salts of potassium may be added to parenteral fluids in concentration of potassium up to 80 mEq./L. Special isotonic solutions of sodium and potassium salts are described.

The cardinal danger of potassium therapy is cardiac arrest due to elevation of the serum potassium concentration. A serum potassium level above 5.3 mEq./L. or renal insufficiency with oliguria are contraindications to administration of the ion.

REFERENCES


1. Darrow, D. C. Disturbances in electrolyte metabolism in man and their management. *Bull. New York Acad. Med.*, 24: 147, 1948.
2. Tarail, R. and Elkinton, J. R. Potassium deficiency and the role of the kidney in its production. *J. Clin. Investigation*, 28: 99, 1949.
3. Danowski, T. S., Peters, J. H., Rathbun, J. C., Quashnock, J. M. and Greenman, L. Studies in diabetic acidosis and coma, with particular emphasis on the retention of administered potassium. *J. Clin. Investigation*, 28: 1, 1949.
4. Howard, J. E. and Carey, R. A. The use of potassium in therapy. *J. Clin. Endocrinol.*, 9: 691, 1949.
5. Elkinton, J. R., Squires, R. D. and Crosley, A. P., Jr. Intracellular cation exchanges in metabolic alkalosis. *J. Clin. Investigation*, (in press).
6. Elkinton, J. R. and Winkler, A. W. Transfers of intracellular potassium in experimental dehydration. *J. Clin. Investigation*, 23: 93, 1944.
7. Black, D. A. K., McCance, R. A. and Young, W. F. A study of dehydration by means of balance experiments. *J. Physiol.*, 102: 406, 1944.
8. Dicker, S. E. Changes in the extracellular and intracellular fluid phases of muscle during starvation and dehydration in adult rats. *Biochem. J.*, 44: 274, 1949.
9. Coller, F. A., Iob, V., Vaughan, H. H., Kalder, N. B. and Moyer, C. A. Translocation of fluid produced by the intravenous administration of isotonic salt solutions in man postoperatively. *Ann. Surg.*, 122: 663, 1945.
10. Darrow, D. C. The retention of electrolyte during recovery from severe dehydration due to diarrhea. *J. Pediat.*, 28: 515, 1946.
11. Harrison, H. E., Harrison, H. C., Tompsett, R. R. and Barr, D. P. Potassium deficiency in a case of lymphosarcoma with the sprue syndrome. *Am. J. Med.*, 2: 131, 1947.
12. Bellet, S., Nadler, C. S., Gazes, P. C. and Lanning, M. Effect of vomiting due to intestinal obstruction on the serum potassium. *Am. J. Med.*, 6: 712, 1949.
13. Thorn, G. W. and Firor, W. M. Desoxycorticosterone acetate therapy in Addison's disease. Clinical considerations. *J. A. M. A.*, 114: 2517, 1940.
14. Thorn, G. W., Garbutt, H. R., Hitchcock, F. A. and Hartman, F. A. The effect of cortin on the sodium, potassium, chloride, inorganic phosphorus and total nitrogen balance in normal subjects and in patients with Addison's disease. *Endocrinology*, 21: 202, 1937.
15. Pearson, O. H. and Eliel, L. P. Postoperative alkalosis and potassium deficiency. *J. Clin. Investigation (Proc.)*, 28: 803, 1949.
16. Elkinton, J. R., Hunt, A. D., Jr., Godfrey, L., McCrory, W. W., Rogerson, A. G. and Stokes, J. Effects of ACTH in patients with collagen and allied diseases. Proc. of the First Clinical ACTH Conference. J. R. Mote, Editor. P. 429. Philadelphia, Toronto, 1950. The Blakiston Co.
17. Power, M. H. and Sprague, R. G. Alkalosis and low plasma potassium in patients receiving adrenocortical steroids or adrenocorticotrophic hormone of the anterior pituitary. Am. Chem. Soc., Abstracts of the 116th meeting, Sept. 18–23, 1949.
18. Pearson, O. H., Eliel, L. P. and Rawson, R. W. Regression of lymphoid tumors in man induced by ACTH and cortisone. Proc. of the First Clinical ACTH Conference. J. R. Mote, Editor, P. 318. Philadelphia, Toronto, 1950. The Blakiston Co.
19. Kepler, E. J., Sprague, R. G., Clagett, O. T., Power, M. H., Mason, H. L. and Rogers, H. M. Adrenal cortical tumor associated with Cushing's syndrome. Report of a case with metabolic studies and remarks on the pathogenesis of Cushing's syndrome. *J. Clin. Endocrinol.*, 8: 499, 1948.
20. Seldin, D. W. and Tarail, R. The metabolism and excretion of electrolytes and glucose in diabetic acidosis. *J. Clin. Investigation (Proc.)*, 28: 810, 1949.
21. Danowski, T. S., Greenman, L., Peters, J. H., Gow, R. and Mateer, F. Metabolic studies in infants during recovery from vomiting. *J. Clin. Investigation (Proc.)*, 28: 777, 1949.
22. Ferrebee, J. W., Gerity, M. K., Atchley, D. W. and Loeb, R. F. Behavior of electrolytes in familial periodic paralysis. *Arch. Neurol. & Psychiat.*, 44: 830, 1940.
23. Danowski, T. S., Elkinton, J. R., Burrows, B. A. and Winkler, A. W. Exchanges of sodium and potassium in familial periodic paralysis. *J. Clin. Investigation*, 27: 65, 1948.
24. Keys, A. The effects in men and dogs of massive doses of insulin on the composition of blood serum. *Am. J. Physiol.*, 123: 608, 1938.
25. Butler, A. M., Talbot, N. B. and MacLachlan, E. A. Effect of testosterone therapy on concentrations of potassium in serum. *Proc. Soc. Exper. Biol. & Med.*, 51: 378, 1942.
26. Seldin, D. W. and Tarail, R. Effect of hypertonic solutions on the metabolism and excretion of electrolytes. *Am. J. Physiol.*, (in press).
27. Darrow, D. C., Schwartz, R., Iannucci, J. F. and Coville, F. The relation of serum bicarbonate

concentration to muscle composition. *J. Clin. Investigation*, 27: 198, 1948.
28. Talbott, J. H. Periodic paralysis; a clinical syndrome. *Medicine*, 20: 85, 1941.
29. Nadler, C. S., Bellet, S. and Lanning, M. Influence of the serum potassium and other electrolytes on the electrocardiogram in diabetic acidosis. *Am. J. Med.*, 5: 838, 1948.
30. Tarail, R. Relation of abnormalities in concentration of serum potassium to electrocardiographic disturbances. *Am. J. Med.*, 5: 828, 1948.
31. Ernstene, A. C. and Proudfit, W. L. Differentiation of the changes in the Q-T interval in hypocalcemia and hypopotassemia. *Am. Heart J.*, 38: 260, 1949.
32. Crismon, J. M., Crismon, C. S., Calabresi, M. and Darrow, D. C. Electrolyte redistribution in cat heart and skeletal muscle in potassium poisoning. *Am. J. Physiol.*, 139: 667, 1943.
33. Govan, C. D., Jr. and Darrow, D. C. The use of potassium chloride in the treatment of the dehydration of diarrhea in infants. *J. Pediat.*, 28: 541, 1946.
34. Nadler, C. S., Bellet, S., Reinhold, J. G. and Lanning, M. Alterations in the serum potassium and their relation to certain constituents of the blood in diabetic acidosis. *Am. J. M. Sc.*, 218: 308, 1949.
35. Sherman, H. C. Chemistry of Food and Nutrition. New York, 1941. The Macmillan Company.
36. Butler, A. M., Talbot, N. B., Burnett, C. H., Stanbury, J. B. and MacLachlan, E. A. Metabolic studies in diabetic coma. *Tr. A. Am. Physicians*, 60: 102, 1947.
37. Butler, A. M., Talbot, N. B., Crawford, J. D., MacLachlan, E. A. and Appleton, J. Parenteral fluid therapy in diarrheal disease. *Am. J. Dis. Child.*, 72: 481, 1946.
38. Danowski, T. S. Newer concepts of the role of potassium in disease. *Am. J. Med.*, 7: 525, 1949.
39. Winkler, A. W., Hoff, H. E. and Smith, P. K. Electrocardiographic changes and concentration of potassium in serum following intravenous injection of potassium chloride. *Am. J. Physiol.*, 124: 478, 1938.
40. Payne, F. E., Bennett, L. L., Burstein, S. G. and Hopper, J., Jr. Manifestations of potassium intoxication in the dog heart-lung preparation. *Federation Proc.*, 8: 125, 1949.
41. Elkinton, J. R., Winkler, A. W. and Danowski, T. S. Transfers of cell sodium and potassium in experimental and clinical conditions. *J. Clin. Investigation*, 27: 74, 1948.
42. Keith, N. M. and Burchell, H. B. Clinical intoxication with potassium: its occurrence in severe renal insufficiency. *Am. J. M. Sc.*, 217: 1, 1949.
43. Elkinton, J. R., Tarail, R. and Peters, J. P. Transfers of potassium in renal insufficiency. *J. Clin. Investigation*, 28: 378, 1949.
44. Engel, F. L., Martin, S. P. and Taylor, H. On the relation of potassium to the neurological manifestations of hypocalcemic tetany. *Bull. Johns Hopkins Hosp.*, 84: 285, 1949.

# Measurement of Body Water Compartments*

MARVIN F. LEVITT, M.D.† *and* MARIO GAUDINO, M.D.
*New York, New York* *Buenos Aires, Argentina*

WATER is the most important component of the living organism. It is distributed between two main compartments, the extracellular and the intracellular. The individual existence of these compartments is assured by the presence of an active selective cell membrane which maintains their separate chemical and physiologic characteristics.

Despite the obvious importance of the variations in the distribution of body water between these two spaces, the methods available have not permitted simple and quantitative analyses of these alterations. Recently, improved methods have been devised which offer several advantages: accurate measurement of the space involved, simplicity and the possibility of serial observations. The goal has been to measure simultaneously and independently the extracellular and total body water volumes and subsequently to calculate the intracellular volume by simple difference.

The measurement of any body water compartment depends upon the use of a substance, usually foreign to the organism, which satisfies the primary criteria of uniform and exclusive distribution throughout the space being measured. If, then, the amount of substance so distributed (Z) and its concentration (C) are known, the volume (V) of the compartment is $V = Z/C$.

When used in the intact animal or human, the substance should ideally also fulfill the following conditions: (1) Fairly rapid and uniform distribution throughout the compartment; (2) no formation or destruction in the organism; (3) no specific influence on body water distribution; (4) slow elimination from the body; (5) no toxicity and (6) accurate and easy determination.

The usual technic involves the single intravenous injection of a known amount of the measuring substance. Immediately after injection the plasma concentration will fall at a rate which is a function of (1) the velocity of diffusion throughout the space being measured and (2) its rate of elimination or metabolism.[1] If diffusion is rapid and elimination slow, uniform distribution will rapidly occur and the plasma level will approach constancy. If a plasma sample is then analyzed, the volume of distribution may be calculated from formula ($V = Z/C$). The volume of distribution of the substance will then be equal to the volume of the compartment being measured, if the stated conditions have been fulfilled.

The methods that have been used for the measurement of the body water compartments will now be considered in more detail.

*Extracellular Fluid Space.* The extracellular space, of which the plasma volume represents about one-third, has great physiologic significance since it represents the true "milieu intérieur" in which the cells are constantly immersed. Its accurate measurement in the intact animal or human has not been feasible, however, because most of the substances so used do not fulfill the primary requisite of absolute exclusion from the cells.

The first attempt to measure this space was made histologically by visual examination of frozen preparations of muscle.[2] The interstitial space thus measured represented 15 to 17 per cent of the total muscle mass. The circumstance that the total chloride obtained in the chemical analysis of muscle, if distributed in that histologic space, yields a chloride concentration identical to that

* Based on work done at the Department of Physiology, New York University College of Medicine, New York, N. Y.
† Now at Mt. Sinai Hospital, New York City.

of the plasma led to the conclusion that all chloride was extracellular.[3] Sodium, on the same presumption, was also considered essentially extracellular in distribution.[4]

Based upon the latter conclusion and the additional assumption that the chloride or sodium concentration was identical throughout the body, estimates of extracellular volume were made by measuring the total body chloride or sodium and the serum concentration, and by applying these values in equation ($V = Z/C$).[4,5] Since this latter procedure demanded sacrifice of the animal, another method was tried which presumably measured changes of the extracellular volume in the intact animal or human. Complicated chloride and sodium balance studies were performed and the data so obtained were used to calculate these alterations.[6] This type of experiment was likewise based upon the assumption of uniform and exclusively extracellular distribution of chloride or sodium. However, it has been shown that both sodium and chloride enter the cells to a variable degree. The sodium/chloride ratio of most tissues in the body, especially bone, cartilage and striated muscle, is higher than that ratio in an ultrafiltrate of plasma.[4,7] This indicates that a certain proportion of sodium is intracellular. Further, in the animal deprived of potassium, sodium will enter the cells in increasing proportions.[8] On the other hand, the ratio of sodium/chloride in gastric and intestinal mucosa, salivary glands, erythrocytes and connective tissue is lower than that same ratio in an ultrafiltrate of plasma, demonstrating that these organs contain a significant quantity of intracellular chloride.[4,7,9] The circumstance that with a constant extracellular volume, the chloride space increases as potassium enters the cells also shows that the chloride space is variably larger than the true extracellular volume.[10,11]

Despite these disadvantages, radioactive chloride and sodium have gained some reputation as measures of the extracellular volume. The former is believed to offer a more valid approximation because of its smaller space of distribution.[12–15] The use of radioactive chloride ($Cl^{38}$) is hampered by its exceptionally short half-life (thirty-seven minutes). On the other hand, radioactive sodium does not completely exchange with the body sodium for at least twenty-four hours although the three-hour space may approximate the total sodium space.[16]

Bromide, since it is distributed in the tissues exactly like chloride, has also been used to measure extracellular volume.[17–19] Obviously, it is subject to the same criticisms.

The most widely used substance for this purpose has probably been sodium thiocyanate.[20–23] It offers the advantages of simplicity of determination, rapid equilibration and extremely slow renal excretion. As originally demonstrated, however, it enters the red cells, gastric mucosa and probably other tissues and was, accordingly, suggested for use only as an index of changes in the extracellular space.[20] This contention has been invalidated by the fact that the cellular permeability to the thiocyanate ion is markedly increased in pathologic states.[24,25] Further, the thiocyanate space is not constant in the same animal under identical conditions.[26] This substance measures a volume variably intermediate between extracellular volume and total body water.[27]

The simultaneous use of thiocyanate, sodium[24] and $Cl^{38}$ has given spaces of distribution of 35.6, 27.6, and 24.7 per cent of body weight, respectively.[28] (Table 1.)

Sulfate has likewise been employed but it presents the disadvantages of very rapid renal excretion and the necessity for corrections due to the endogenous serum sulfate as well as endogenous sulfate excretion.[29–31]

To obviate the disadvantage of the variable entrance of electrolytes into the cells, substances were sought to which the cell membrane was impermeable. The carbohydrates sucrose,[29,30] mannitol[32–34] and inulin[10,35] were studied. They offered smaller spaces of distribution and presumably more accurate indices of the extracellular volume. However, they presented the problem of more difficult analytic methods, rapid renal excretion and, in the case of mannitol and sucrose, incomplete urinary recovery, indi-

cating some degree of utilization for which no simple correction could be made.[33,36,37]

The properties of inulin offer many advantages over any of the above substances. It is not an electrolyte, is lipoid-insoluble and has a large molecular weight (about 5,000), all circumstances that reduce the probability of its permeating the cell membrane. It does not penetrate the erythrocyte,[38] diffuse through the renal tubule,[38–40] or undergo concentration by liver cells.[41] Its rapid and quantitative recovery in the urine[37,40,42] argues against its being metabolized to any appreciable degree or stored in any tissue. Furthermore, it is physiologically inert and exerts negligible osmotic pressure,[40,43] a situation that will prevent its drawing water from the cells. However, it has the prime disadvantage of rapid glomerular excretion, which prevents uniform distribution throughout the extracellular space when given by the usual single injection method. This has previously limited its use to the nephrectomized animal in which the volume of distribution of inulin is significantly smaller than that of chloride or thiocyanate.[10,35]

The disadvantage of the rapid renal excretion of inulin has been overcome by an equilibration method which permits its use in the intact animal or man.[42,44,45] This procedure depends upon the maintenance of a steady infusion which compensates for the renal excretion of inulin and maintains the plasma level constant until uniform concentration exists throughout the entire extracellular space. Once equilibrium is established a blood sample is withdrawn, the bladder is emptied by catheter and rinsed and the infusion simultaneously discontinued. The urine is then collected until the total amount of inulin contained within the body is excreted (five hours in the dog, twelve hours in man). The quantity of inulin recovered (mg.) divided by the plasma concentration (mg./cc.) prior to the cessation of the infusion equals the volume of distribution (cc.).* (Fig. 1.)

The length of infusion necessary to insure uniform distribution of inulin throughout the extracellular volume is two hours in the dog and five hours in man. This time has been established empirically in the intact dog or human by determining that minimal infusion time prolongation of which will not

TABLE I

VOLUMES OF DISTRIBUTION OF SUBSTANCES USED TO MEASURE BODY WATER COMPARTMENTS*

| Dog | | Man | |
|---|---|---|---|
| Extracellular Fluid Volume (% of body weight) | | Extracellular Fluid Volume (% of body weight) | |
| Inulin | 20,[42] 19[44] | Inulin | 16,[42] 15,[47] 16[45] |
| Sucrose | | Sucrose | 20,[29] 19[30] |
| Mannitol | | Mannitol | 23,[34] 18,[32] 16[33]† |
| Chloride | 27,[4] 23,[9] 25[28] | Chloride | 18[51] |
| Bromide | 31,[7] 30[42] | Bromide | 27,[17] 23[45] |
| Sulfate | 26[50] | Sulfate | 20,[29] 24[30] |
| Sodium | 28,[28] 30,[42] 30[44] | Sodium | 26,[51] 26,[15] 26[45] |
| Thiocyanate | 32,[19] 30,[48] 36,[28] 32,[42] 34[44] | Thiocyanate | 22,[29] 23,[30] 27,[51] 25,[15] 22,[42] 24,[19] 24[45] |
| Total Body Water (% of body weight) | | Total Body Water (% of body weight) | |
| Total desiccation | 60[4] | Total desiccation | 68[52] |
| Deuterium oxide | 63[44] | Deuterium oxide | 63,[70] 72,[51] 53[82] |
| Antipyrine | | Antipyrine | 55,[47] 52[82] |

* Those values with the same reference numbers represent simultaneous determinations.
† Corrected for the metabolism of mannitol.

* The accuracy obtained by subtracting the total amount of inulin excreted from the total injected during the equilibrating infusion is not adequate.

increase the space of distribution of inulin. These values were confirmed by the single injection method in the nephrectomized dog and an anuric patient.[42,44]

The amount of inulin contained within the dead space* of the kidney at the moment

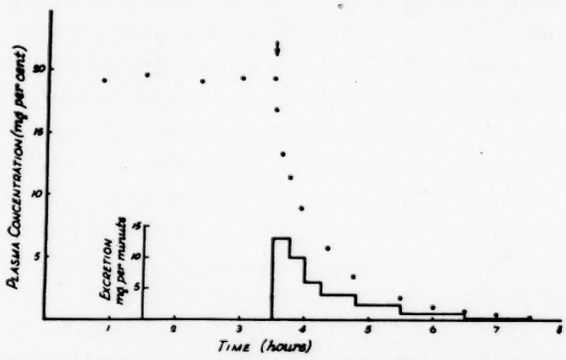



FIG. 1. Experiment illustrating inulin space determination in the dog; at the instant designated by the arrow a plasma sample is obtained, the constant infusion is discontinued and the bladder is emptied and rinsed. Subsequently, all the urine is saved until the inulin has been completely excreted.

that the bladder is washed may introduce an error into the calculation of the inulin space. This error may be significant if the urine flow is less than 2 cc./minute but the amount of inulin so located may be determined experimentally and a correction made. (Fig. 2.) With urine flows above 3 cc./minute no correction is necessary.[44]

The inulin space or extracellular volume thus determined averages 19.4 per cent of body weight in the dog and 16 per cent in the human.[42,44,45] These values have been found to be remarkably constant under normal conditions from day to day. That the infusion method has accomplished total and uniform distribution of inulin in the intact animal has been corroborated by the identity of the spaces so obtained with those determined by the single injection method in the same animal after complete nephrectomy.[44]

The circumstance that the inulin space affords the lowest value of extracellular fluid yet recorded, plus the evidence that all substances previously used are now known to enter the cells or to be partially metabolized, favors the conclusion that inulin represents the best measure of extracellular fluid available. The only other alternatives are (1) inulin diffuses incompletely in the extracellular space and (2) the extracellular volume may be compartmentalized with only one portion accessible to the inulin molecule. The possibility of incomplete diffusion is negated by the fact that prolongation of the infusion beyond the time necessary for equilibration does not increase the space of distribution.[44,45] To presume that after two hours of infusion incomplete diffusion exists, but that after twelve hours there is no further distribution of inulin, is contradictory. The second alternative is rendered unlikely in view of the identical distribution of sucrose and inulin, substances of markedly different molecular weights, in the nephrectomized rabbit and rat.[10,46] In the human the inulin space agrees with the mannitol space, provided adequate correction is made for the metabolism of mannitol.[33,42] (Table 1.) The identity of the spaces of distribution of molecules

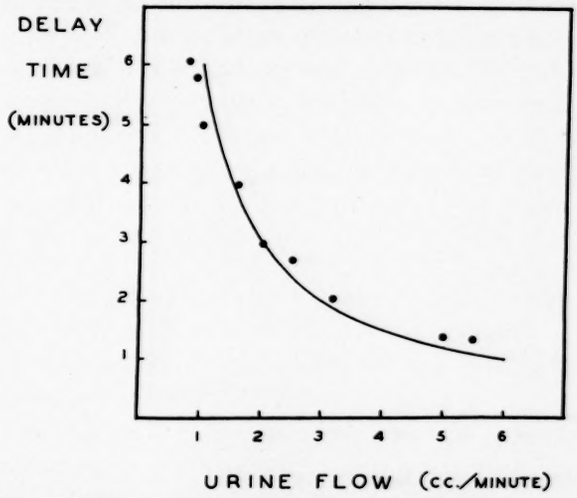



FIG. 2. The curve demonstrates the relation between urine flow and delay time in the dog.[44] The latter represents the approximate time necessary for an inulin molecule to traverse the renal dead space. For a given urine flow the delay time may thus be estimated. The product of delay time and rate of inulin excretion (mg./minute) equals that amount of inulin which must be subtracted from the total recovery before the inulin space is calculated.

* The renal dead space is that portion of the urinary tract between the glomerular membrane and the bladder (tubules, pelves and ureters).

of varying size is strong evidence against any possibility of compartmentalization of the extracellular space. Consequently, the volume of distribution of inulin is equal to the extracellular volume.

The volumes of distribution of all substances previously used for the measure of extracellular volume, expressed as per cent of body weight, are recorded in Table 1. Considering the inulin space as the extracellular volume, the variable intracellular distribution of the other substances may be calculated; almost one-half of the thiocyanate is located within the cells whereas about one-third of the total body sodium and one-fourth of the chloride are intracellular.

*Total Body Water.* The earliest methods available for the measurement of total body water depended upon the total or partial desiccation of the organism.[52] The obvious limitations of this procedure led to a search for a more practicable approach in the intact animal or man.

Newburgh[53] attempted to study total body water exchange by obtaining an accurate account of all sources of water intake as well as all the avenues of excretion. Water lost by evaporation, water set free by tissue combustion and water released by oxidation of food were considered. The errors involved make this method quite impracticable.[54]

From the observation that the total base and water excreted are in the same proportion as they appear in the plasma Gamble[55] concluded that the concentration of the cations was the same all over the body, and that this concentration remained constant despite variations in the volume of total body water. It was thus suggested that the water exchange could be estimated from cation balance studies. It was assumed that all the base in the body existed in an ionized form in simple solution. This method demands tedious balance experiments subject to frequent errors. Furthermore, some of its basic assumptions have been contested.[56]

Attempts have been made to measure total body water by determining the specific gravity of the whole body.[57–59] This was based upon an empirical equation derived from the simultaneous and independent measurement of the body specific gravity, total body water and body fat in the sacrificed animal.[57,59] Accurate measurement of the body specific gravity in the living organism, however, is complicated by the presence of gases in the respiratory system and gastrointestinal tract. In addition, there is no evidence that the empirical formula used may be applicable during all physiologic and pathologic variations.

Several substances[60–63] recommended for use according to the general dilution method have been discarded because of their failure to fulfill the necessary conditions for the measurement of total body water. Urea, thiourea and sulfanilamide have all been found to be unequally distributed in body tissues, urea presenting the additional disadvantage of significant variation in endogenous formation.[64–68] The use of potassium[69] has likewise been questioned because of overwhelming evidence that the cells are able to concentrate this ion actively.[2]

Deuterium oxide ($D_2O$), on the basis of its similarity both biologically and chemically to $H_2O$, appears to be the ideal substance for the measure of total body water.[70] It is non-toxic[70] and can be quantitatively detected.[71] It offers the advantage of very rapid diffusion through the cell membrane[72–75] and complete equilibrium is rapidly attained after a single injection. The time necessary for this equilibrium is nine minutes in the guinea pig,[76] eight to thirty minutes in the rabbit,[77] fifteen to twenty minutes in the dog[78] and one hour in man.[51] Equilibration between plasma, red blood cells and other tissues occurs very rapidly *in vitro* and *in vivo*.[73–75,79] It has been shown that the human kidney does not concentrate heavy water and the presumption has been made that the concentration of this substance in urine and plasma is identical.[70] The rate of elimination of $D_2O$ from the human body is extremely slow: about one-half of the total amount introduced is excreted after nine days. Furthermore, in man, after equilibrium is reached, the

plasma concentration remains constant for nineteen hours.[56]

A certain proportion of the deuterium atoms may interchange with the hydrogen atoms in the organic compounds within the body (other than water)[80,81] but this fraction has been estimated to be very small. Moore has calculated that of the total heavy water injected, no more than 5 per cent of the deuterium atoms will enter metabolic processes.[51]

That the volume of distribution of heavy water is identical with the total body water in the living animal has been demonstrated by comparing the values so obtained with those determined by the total desiccation of the animal. In the rabbit these two volumes have been found to agree within 5 per cent.[51] The total body water as measured with $D_2O$ averages 65 per cent of the body weight in the guinea pig,[76] 66 per cent in the rabbit,[77] 63 per cent in the dog,[44] 53 per cent in man.[82]

The radioactive isotope of hydrogen, tritium, in the form of THO, has also been employed to measure total body water.[83] Equilibrium after intravenous injection is established in the rabbit in thirty minutes, and close agreement between tritium space and body water after desiccation has been found.[83] In man equilibrium is established after one hour, with a space of distribution of 64.8 per cent of body weight.[83] The use of tritium, however, requires elaborate procedures for preparation and quantitation.

Recently, it has been demonstrated that antipyrine is uniformly distributed throughout the body water after a single injection and its use as a measuring agent has been recommended.[82] Simultaneous heavy water and antipyrine spaces in the human show fairly good correlation even though values obtained with the former are slightly higher.[82] Although antipyrine offers a method which is much simpler and cheaper than the use of heavy water, it presents certain disadvantages: (1) A small amount of antipyrine is bound to plasma protein for which no exact correction can be made. (2) Antipyrine is metabolized, presumably at a constant rate, so that plasma concentrations must be extrapolated to time zero for the proper correction. (3) In the hydropic patient the discrepancy between the heavy water space and the antipyrine space is greater than in the normal although in the same direction. (4) Tissue analysis reveals that lung, kidney and liver do not attain concentrations identical with plasma.[82] The use of antipyrine therefore requires further evaluation.

## CONCLUSION

The use of inulin and heavy water or possibly antipyrine permits the simultaneous measurement of the extracellular compartment, total body water and, by difference, the intracellular space. In man these three compartments have been shown to represent 16 per cent, 53 per cent and 37 per cent of body weight, respectively. If these methods are coupled with the measurement of total body anion or cation by means of radioactive tracer studies, it becomes feasible to estimate the average intracellular electrolyte concentration in the intact animal or man.[16] It has already been demonstrated that these methods may be applied in the study of physiologic and pathologic alterations of body water and electrolyte distribution.[27]

## REFERENCES

1. Gaudino, M. Kinetics of distribution of inulin between two body water compartments. *Proc. Soc. Exper. Biol. & Med.*, 70: 672, 1949.
2. Fenn, W. O. Electrolytes in muscle. *Physiol. Rev.*, 16: 450, 1936.
3. Fenn, W. O., Cobb, D. M. and Marsh, B. S. Sodium and chloride in frog muscle. *Am. J. Physiol.*, 110: 261, 1934.
4. Harrison, H. E., Darrow, D. C. and Yannet, H. The total electrolyte content of animals and its probable relation to the distribution of body water. *J. Biol. Chem.*, 113: 515, 1936.
5. Hastings, A. and Eichelberger, L. The exchange of salt and water between muscle and blood. I. The effect of an increase of total body water produced by the intravenous injection of isotonic salt solutions. *J. Biol. Chem.*, 117: 73, 1937.
6. Lavietes, P. H., D'Esopo, L. M. and Harrison, H. E. The water and base balance of the body. *J. Clin. Investigation*, 14: 251, 1935.
7. Manery, J. F. and Hastings, A. B. The distribution of electrolytes in mammalian tissues. *J. Biol. Chem.*, 127: 657, 1939.
8. Heppel, L. A. The electrolytes of muscle and liver in

potassium depleted rats. *Am. J. Physiol.*, 127: 385, 1939.

9. Amberson, W. R., Nash, T. P., Mulder, A. G. and Binns, D. The relationship between tissue chloride and plasma chloride. *Am. J. Physiol.*, 122: 224, 1938.
10. Wilde, W. S. The chloride equilibrium in muscle. *Am. J. Physiol.*, 143: 666, 1945.
11. Boyle, P. J. and Conway, E. J. Potassium accumulation in muscle and associated changes. *J. Physiol.*, 100: 1, 1941.
12. Manery, J. F. The fate of injected radioactive chloride. *Am. J. Physiol.*, 129: 417, 1940.
13. Manery, J. F. and Bale, W. F. The penetration of radioactive sodium and phosphorus into the extra- and intracellular phases of tissues. *Am. J. Physiol.*, 132: 215, 1941.
14. Manery, J. F. and Haege, L. F. The extent to which radioactive chloride penetrates tissues, and its significance. *Am. J. Physiol.*, 134: 83, 1941.
15. Kaltreider, N. L., Meneely, G. R., Allen, J. R. and Bale, W. F. Determination of the volume of the extracellular fluid of the body with radioactive sodium. *J. Exper. Med.*, 74: 569, 1941.
16. Levitt, M. F. and Gaudino, M. Use of radioactive isotopes to measure intracellular cation concentrations in the normal dog. *Am. J. Physiol.*, 159: 67, 1949.
17. Brodie, B. B., Brand, E. and Leshin, S. The use of bromide as a measure of extracellular fluid. *J. Biol. Chem.*, 130: 555, 1939.
18. Wallace, G. B. and Brodie, B. B. The distribution of administered bromide in comparison with chloride and its relation to body fluids. *J. Pharmacol. & Exper. Therap.*, 65: 214, 1939.
19. Goudsmit, A., Louis, L. and Scott, J. C. Bromide space, thiocyanate space and the measurement of extracellular fluid volume. *Am. J. Physiol.*, 133: 297, 1941.
20. Crandall, L. A. and Anderson, M. X. Estimation of the state of hydration of the body by the amount of water available for the solution of sodium thiocyanate. *Am. J. Digest. Dis.*, 1: 126, 1934–35.
21. Ashworth, C. T., Muirhead, E. E., Thomas, O. F. and Hill, J. M. An analysis of the thiocyanate method for determining the distribution of the body fluids. *Am. J. Physiol.*, 139: 255, 1943.
22. Elkinton, J. R. and Taffel, M. The apparent volume of distribution of sulfocyanate and of sulfanilamide in the dog. *Am. J. Physiol.*, 138: 126, 1942–43.
23. Gregersen, M. I. and Stewart, J. D. Simultaneous determination of the plasma volume with T-1824, and the "available fluid" volume with sodium thiocyanate. *Am. J. Physiol.*, 125: 142, 1939.
24. Overman, R. R. Permeability alterations in disease. *J. Lab. & Clin. Med.*, 31: 1170, 1946.
25. Overman, R. R. and Feldman, H. A. The effect of fatal "P. Knowlesi" malaria on simian circulatory and body fluid compartment physiology. *J. Clin. Investigation*, 27: 1049, 1947.
26. Gaudino, M. and Levitt, M. F. Unpublished observations.
27. Gaudino, M. and Levitt, M. F. Influence of the adrenal cortex on body water distribution and renal function. *J. Clin. Investigation*, 28: 1487, 1949.
28. Winkler, A. W., Elkinton, J. R. and Eisenman, A. J. Comparison of sulfocyanate with radioactive chloride and sodium in the measurement of extracellular fluid. *Am. J. Physiol.*, 139: 239, 1943.
29. Lavietes, P. H., Bourdillon, J. and Peters, J. P. The volume of the extracellular fluids. *J. Clin. Investigation*, 14: 705, 1935.
30. Lavietes, P. H., Bourdillon, J. and Klinghoffer, K. A. The volume of the extracellular fluids of the body. *J. Clin. Investigation*, 15: 261, 1936.
31. Peters, J. P. Transfers of water and solutes in the body. *Harvey Lect.*, 33: 112, 1937–38.
32. Newman, E. V., Bordley, J. and Winternitz, J. The interrelationships of glomerular filtration rate (mannitol clearance), extracellular fluid volume, surface area of the body and plasma concentration of mannitol. *Bull. Johns Hopkins Hosp.*, 75: 253, 1944.
33. Dominguez, R., Corcoran, A. C. and Page, I. H. Mannitol: kinetics of distribution, excretion and utilization in human beings. *J. Lab. & Clin. Med.*, 32: 1192, 1947.
34. Elkinton, J. R. The volume of distribution of mannitol as a measure of the volume of extracellular fluid, with a study of the mannitol method. *J. Clin. Investigation*, 27: 1088, 1947.
35. Kruhöffer, P. Inulin as an indicator for the extracellular space. *Acta physiol. Scandinav.*, 11: 16, 1946.
36. Keith, N. M. and Power, M. H. The urinary excretion of sucrose and its distribution in the blood after intravenous injection into normal man. *Am. J. Physiol.*, 120: 203, 1937.
37. Smith, W. W., Finkelstein, N. and Smith, H. W. Renal excretion of hexitols (sorbitol, mannitol and dulcitol) and their derivatives (sorbitan, isomannide and sorbide) and of endogenous creatinine-like chromogen in dog and man. *J. Biol. Chem.*, 135: 231, 1940.
38. Smith, H. W. Physiology of the Kidney. New York, 1937. Oxford Univ. Press.
39. Richards, A. N., Westfall, B. B. and Bott, P. A. Renal excretion of inulin, creatinine and xylose in normal dogs. *Proc. Soc. Exper. Biol. & Med.*, 32: 73, 1934.
40. Shannon, J. A. and Smith, H. W. The excretion of inulin, xylose and urea by normal and phlorizinized man. *J. Clin. Investigation*, 14: 343, 1935.
41. Haywood, C. and Höber, R. The permeability of the frog liver to certain lipoid and insoluble substances. *J. Cell. & Comp. Physiol.*, 10: 305, 1937.
42. Gaudino, M., Schwartz, I. L. and Levitt, M. F. Inulin volume of distribution as a measure of extracellular fluid in dog and man. *Proc. Soc. Exper. Biol. & Med.*, 68: 507, 1948.
43. Smith, H. W., Chasis, H. and Ranges, H. Suitability of inulin for intravenous administration to man. *Proc. Soc. Exper. Biol. & Med.*, 37: 726, 1938.
44. Gaudino, M. and Levitt, M. F. Inulin space as a measure of extracellular fluid. *Am. J. Physiol.*, 157: 387, 1949.
45. Schwartz, I. L., Schacter, D. and Freinkel, N. The measurement of extracellular fluid in man by means of a constant infusion technique. *J. Clin. Investigation*, 28: 1117, 1949.
46. Kruhöffer, P. The significance of diffusion and convection for the distribution of solutes in the

interstitial space. *Acta physiol. Scandinav.*, 11: 37, 1946.

47. Berger, E. Y., Dunning, M. F., Brodie, B. B. and Steele, J. M. Body water compartments in man. *Federation Proc.*, 8: 10, 1949.
48. Sunderman, F. W. and Dohan, F. C. Distribution of water and electrolytes in experimental diabetes mellitus. *Am. J. Physiol.*, 132: 418, 1941.
49. Mellors, R. C., Muntwyler, E., Mautz, F. R. and Abbott, W. E. Changes in the plasma volume and "available (thiocyanate) fluid" in experimental dehydration. *J. Biol. Chem.*, 144: 785, 1942.
50. Smith, P. K., Winkler, A. W. and Schwartz, B. M. The distribution of magnesium following the parenteral administration of magnesium sulfate. *J. Biol. Chem.*, 129: 51, 1939.
51. Moore, F. D. Determination of total body water and solids with isotopes. *Science*, 104: 157, 1946.
52. Mitchell, H. H., Hamilton, T. S., Steggerda, F. R. and Bean, H. W. The chemical composition of the adult human body and its bearing on the biochemistry of growth. *J. Biol. Chem.*, 158: 625, 1945.
53. Newburgh, L. H., Johnston, M. W. and Falcon-Lesses, M. Measurement of total water exchange. *J. Clin. Investigation*, 8: 161, 1930.
54. Lavietes, P. H. The metabolic measurement of the water exchange. *J. Clin. Investigation*, 14: 57, 1935.
55. Gamble, J. L., Ross, G. S. and Tisdall, F. F. The metabolism of fixed base during fasting. *J. Biol. Chem.*, 57: 633, 1923.
56. Elkinton, J. R., Winkler, A. W. and Danowski, T. S. Inactive cell base and the measurement of changes in cell water. *Yale J. Biol. & Med.*, 17: 383, 1944–45.
57. Rathbun, R. N. and Pace, N. Studies on body composition. I. The determination of total body fat by means of the body specific gravity. *J. Biol. Chem.*, 158: 667, 1945.
58. Morales, M. F., Rathbun, E. N., Smith, R. E. and Pace, N. Studies on body composition. II. Theoretical considerations regarding the major body tissue components, with suggestions for application to man. *J. Biol. Chem.*, 158: 677, 1945.
59. Pace, N. and Rathbun, E. N. Studies on body composition. III. The body water and chemically combined nitrogen content in relation to fat content. *J. Biol. Chem.*, 158: 685, 1945.
60. Marshall, E. K., Emerson, K. and Cutting, W. C. The distribution of sulfanilamide in the organism. *J. Pharmacol. & Exper. Therap.*, 61: 196, 1937.
61. Painter, E. E. Simultaneous determinations of the body water available for dilution of exogenous urea and sulfanilamide in unanesthetized dogs. *Am. J. Physiol.*, 123: 159, 1938.
62. Painter, E. E. Total body water in the dog. *Am. J. Physiol.*, 129: 744, 1940.
63. Danowski, T. S. Use of thiourea as a measure of change in body water. *J. Biol. Chem.*, 152: 207, 1944.
64. Sise, H. S. Distribution of sulfanilamide and acetylsulfanilamide between cells and extracellular fluid. *Proc. Soc. Exper. Biol. & Med.*, 40: 451, 1939.
65. Waterhouse, A. and Shannon, J. A. On the use of sulfanilamide in measurement of body water in the dog. *Proc. Soc. Exper. Biol. & Med.*, 50: 189, 1942.
66. Ralls, J. O. Urea is not equally distributed between the water of the blood cells and that of the plasma. *J. Biol. Chem.*, 151: 529, 1943.
67. Chesley, L. C. Observations on the absorption, apparent volume of distribution and excretion of thiourea. *J. Clin. Investigation*, 23: 856, 1944.
68. Williams, R. H. and Kay, G. A. Absorption, distribution and excretion of thiourea. *Am. J. Physiol.*, 143: 715, 1945.
69. Winkler, A. W. and Smith, P. K. The apparent volume of distribution of potassium injected intravenously. *J. Biol. Chem.*, 124: 589, 1938.
70. Hevesy, G. and Hofer, E. Elimination of water from the human body. *Nature*, 134: 879, 1934.
71. Keston, A. S., Rittenberg, D. and Schoenheimer, R. Determination of deuterium in organic compounds. *J. Biol. Chem.*, 122: 227, 1937–38.
72. Lucke, B. and Harvey, E. N. The permeability of living cells to heavy water (deuterium oxide). *J. Cell. & Comp. Physiol.*, 5: 473, 1934–35.
73. Brooks, S. C. The permeability of erythrocytes to deuterium oxide (heavy water). *J. Cell. & Comp. Physiol.*, 7: 163, 1935–36.
74. Parpart, A. K. The permeability of the mammalian erythrocyte to deuterium oxide (heavy water). *J. Cell. & Comp. Physiol.*, 7: 153, 1935–36.
75. Govaerts, J. and Lambrechts, A. Penetration of water into erythrocytes with heavy water as indicator. *Nature*, 157: 301, 1946.
76. Flexner, L. B., Gellhorn, A. and Merrell, M. Studies on rates of exchange of substances between the blood and extravascular fluid. I. The exchange of water in the guinea pig. *J. Biol. Chem.*, 144: 35, 1942.
77. Hevesy, G. and Jacobsen, C. F. Rate of passage of water through capillary and cell walls. *Acta physiol. Scandinav.*, 1: 11, 1940–41.
78. Levitt, M. F. and Gaudino, M. Unpublished observations.
79. Krogh, A. and Ussing, H. H. Cited by Hevesy, G. Radioactive Indicators. New York, 1948. Interscience Publishers, Inc.
80. Ussing, H. H. The exchange of H and D atoms between water and protein in vivo and in vitro. *Skandinav. Arch. f. Physiol.*, 78: 225, 1938.
81. Krogh, A. and Ussing, H. H. The exchange of hydrogen between the free water and the organic substances in the living organism. *Skandinav. Arch. f. Physiol.*, 75: 90, 1936–37.
82. Soberman, R., Brodie, B. B., Levy, B. B., Axelrod, J., Hollander, V. and Steele, J. M. The use of antipyrine in the measurement of total body water in man. *J. Biol. Chem.*, 179: 31, 1949.
83. Pace, N., Kline, L., Schachman, H. W. and Harfenist, M. Studies on body composition. IV. Use of radioactive hydrogen for measurement *in vivo* of total body water. *J. Biol. Chem.*, 68: 459, 1947.

# Seminars on Renal Physiology

## Significance of the Renal Juxtamedullary Circulation in Man*

MORTON H. MAXWELL, M.D., ERNEST S. BREED, M.D. *and* HOMER W. SMITH, SC.D.
*New York, New York*

IN 1947 Trueta, Barclay, Daniel, Franklin and Prichard[1] pointed out that during renal ischemia induced by a variety of means in experimental animals, notably rabbits, the renal cortex may be devoid of blood at a time when the juxtamedullary glomeruli (i.e., those adjacent to the medulla) may still be undergoing perfusion. Anatomic studies led the authors to suggest that the juxtamedullary glomeruli afford a by-pass by which blood is diverted from the renal arteries to the renal veins without exposure to the cortical parenchyma. These studies have raised the question of whether such a shunting mechanism exists in man and, if so, what its significance may be in various states of disturbed renal function.

The present paper comprises a review of the literature and a report on observations on the renal circulation in man pertinent to this problem.

### ANATOMY

Figure 1 presents the cardinal features of the cortical and juxtamedullary circulation as described by Trueta and his colleagues. These investigators agree with the opinion of most anatomists that normally the mammalian renal blood supply is exclusively glomerular. They emphasize, however, that blood reaching the kidney has two potential routes through that organ, involving basically different types of vasculonephric units. These two routes diverge from the interlobular arteries at the junction of the inner one-third and outer two-thirds of the renal cortex, i.e., at the approximate dividing line between juxtamedullary and cortical glomeruli, respectively.

Distinction must be made between these two types of nephrons with respect to two points:

*Fate of Postglomerular Blood.* The efferent arteriole of the typical cortical glomerulus is much smaller than the afferent arteriole, whereas in a juxtamedullary glomerulus the efferent arteriole is as large as, or at times even larger, than the afferent arteriole. The efferent arteriole of the cortical glomerulus breaks up into capillaries of small caliber which are distributed around the proximal and distal tubules as well as most of the loop of Henle, forming the intertubular capillary network and emptying into an interlobular vein. The efferent vessel of a juxtamedullary glomerulus, on the other hand, proceeds as a single large trunk into the medulla where it divides into a group of straight parallel vessels, the *vasa recta*, the individual caliber of which is but little less than that of the efferent arteriole itself. The *vasa recta* are identical in structure with capillaries elsewhere in the kidney but they differ from both cortical and systemic capillaries in that they have a larger caliber, the venous components are larger than the arterial components, they pass in an essentially straight line from the glomerulus toward the medullary papilla to loop back toward the cortex where they end in an arcuate or interlobular

* From the Departments of Physiology, Surgery and Medicine, New York University College of Medicine, and the Third Medical and Surgical Divisions of Bellevue Hospital, New York, N. Y. Aided by a grant from the Commonwealth Fund.

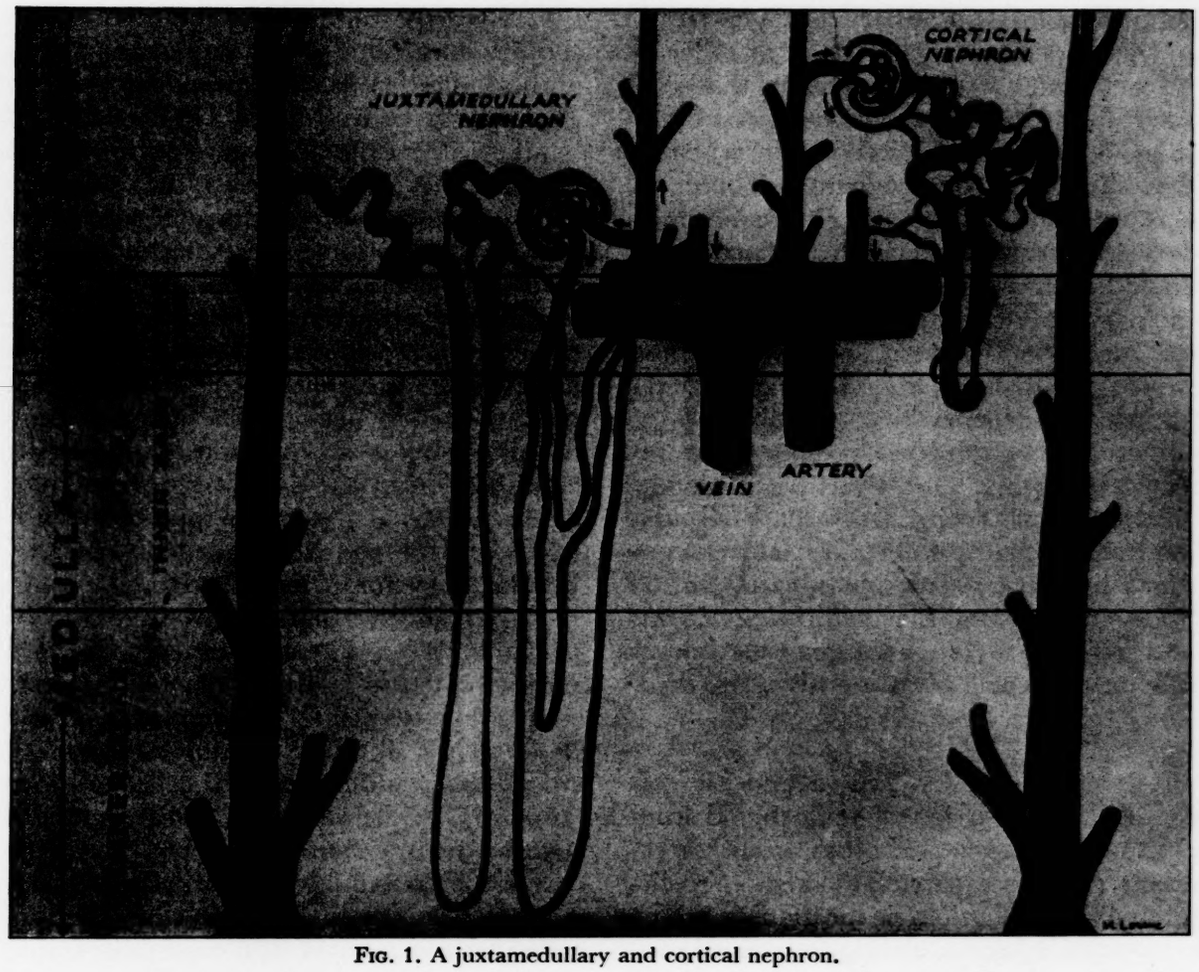



FIG. 1. A juxtamedullary and cortical nephron.

vein, and they tend to be grouped together in compact bundles around or adjacent to the thin limb of the loop of Henle.

*Loob of Henle.* As Peter first demonstrated in 1909,[2] the loop of Henle in those tubules arising from the cortical glomeruli passes only a relatively short distance into the medulla, the thin segment of this loop being very short. On the other hand, the loop of Henle in the tubules of the juxtamedullary glomeruli descends deeply into the medulla, often as far as the papilla, the greater part of the loop within the medulla being made up by the thin segment. Thus in the deepest part of the medulla the thin segments are in juxtaposition to the *vasa recta* alone.*

These writers occasionally mention (usually parenthetically) a small and inconstant capillary supply from the efferent arterioles of the juxtamedullary glomeruli and from the most proximal parts of the *vasa recta*, these capillaries presumably supplying some of the convoluted tubules in the juxtamedullary zone. But the functional importance of these capillaries is discounted in the final argument, "It will thus be seen that the *vasa recta* provide a pathway of considerable capacity, which makes it possible for the blood to pass from the 'arcuate' and proximal parts of the interlobular arteries, via the juxtamedullary glomeruli, to the corre-

* An anatomic point which Trueta et al. tend to disregard is that the outer third of the medulla contains, in addition to thin segments of both cortical and juxtamedullary nephrons, the straight descending limb of the proximal tubule and the straight ascending limb of the distal tubule of the juxtamedullary nephrons. In this region, therefore, the *vasa recta* have functional relation to proximal and distal tubule tissue as does the capillary circulation in the cortex.

sponding veins without traversing a capillary network."

Trueta and his colleagues report that they found no evidence of arteriovenous anastomoses in the normal kidney of any species. They specifically deny Spanner's[3] observations and state that Spanner probably mistook certain coiled arterial twigs for arteriovenous anastomoses. All previously reported aglomerular vessels, such as *arteriae recta verae* and Isaacs-Ludwig arterioles, are explained by them as representing the end product of degenerative canalization of glomeruli as a result of prolonged or repeated juxtamedullary diversion of blood.

Perfusion of the juxtamedullary circulation during cortical ischemia has been confirmed in part by some investigators in the rabbit[4–9] but has failed of confirmation in this species by others.[9–11] In the dog experiments have on the whole been negative.[8,9,12–15]

## PHYSIOLOGY

It is postulated by Trueta and his colleagues that diversion of renal blood from its usual cortical route through the less resistant and more capacious medullary circuit may be a physiologic mechanism which is involved in reflex anuria, the anuria associated with incompatible blood transfusions, crush injury, blackwater fever, etc., humoral (pitressin) inhibition of water diuresis, the renal ischemia of shock or that induced by fright or by adrenalin, in the reduction in tubular excretion following protracted renal ischemia and in the genesis of essential hypertension.

An abundance of evidence is available which appears to refute this interpretation in man and probably in the dog. Consideration of this evidence requires a brief restatement of the functions attributed to various segments of the nephron. On the positive evidence of Marshall,[16] Chambers and Kempton,[17] Cameron and Chambers[18] and Forster[19] the proximal segment, which appears to be homologous in all vertebrates, is the site of tubular excretion of phenol red and other substances which undergo tubular excretion; whereas the distal tubule, at least in tissue culture, is not involved in tubular excretion.[17,18] By equation of their mutual interference in tubular transport, phenol red, diodrast and PAH are excreted by the same cells and same segment. No evidence has been adduced that the thin segment of the loop of Henle is capable of excreting PAH or other substances. The cytologic structure of the epithelium of this segment argues against such a view, and the presently accepted interpretation based on somewhat indirect evidence[20] indicates that it is interposed between the proximal and distal segments to promote the osmotic equilibration of the urine before the latter enters the distal system for final concentration. For complete clearance of PAH by tubular excretion it may therefore be inferred that all the blood must in effect be presented to proximal tissue. Because it is not presented to proximal tissue, any blood exclusively perfusing the *vasa recta* should have a low PAH extraction ratio ($E_{PAH}$) since this value would be determined primarily by the extent of filtration in the juxtamedullary glomeruli.

The juxtamedullary glomeruli in elderly normal persons, in subjects with essential hypertension, and in other conditions presumably involving protracted or repeated juxtamedullary diversion, are stated by Trueta and his colleagues to be canalized by degenerative vascular changes* with

* The Trueta monograph devotes considerable discussion to the evolution and significance of these degenerate juxtamedullary glomeruli. Their explanation is as follows: "The excessive operation of the mechanism by which blood is diverted from the cortex through the medullary by-pass causes an initial dilatation of one of the capillary loops of the juxtamedullary glomerulus, probably a loop that is shorter and broader than the others. When the by-passing mechanism next operates, this dilated capillary carries more of the glomerular blood than any other capillaries of the glomerulus, and in consequence becomes even more dilated, to carry still more of the glomerular blood flow when the by-passing mechanism next operates. This sequence of events, frequently repeated, leads inevitably to a final, permanent, gross dilatation of the affected capillary, and at the same time to the atrophy of all the other capillary loops of the glomerular tuft.

"In this final stage, the afferent and efferent vessels, united by a grossly dilated 'capillary,' form a single continuous trunk of large calibre, and thereby provide a direct and wide pathway to the vasa recta."

consequent reduction in filtering surface. Therefore, diversion of blood through these channels should reduce the extraction ratio of inulin ($E_{IN}$) and result in a marked reduction in the inulin clearance ($C_{IN}$).

These investigators report that during renal ischemia the arterial pulse may be seen in the renal vein, and the renal venous blood may in whole or in part acquire an arterial color, indicating that the juxtamedullary glomeruli may afford veritable shunts between the renal artery and renal vein. They offer as an explanation for the unreduced state of the renal venous blood ". . . a diversion of the blood from the cortex, the most active part of the kidney, to the medullary pathway, with a possibly increased speed of flow through these channels." Such shunts should therefore cause a reduction in renal oxygen A-V difference.

Reduction in $E_{PAH}$ alone during renal ischemia is not final evidence of a juxtamedullary shunt since anoxic injury of the proximal tubules would have the same effect. Reduction of $E_{IN}$ alone during renal ischemia is not final evidence of such a shunt or of canalized glomeruli, since reduction of glomerular pressure would have the same effect. A combination of these two changes is scarcely better evidence, since anoxia and reduced glomerular pressure can and indeed are apt to occur together. Better evidence of a shunt would be reduction in both $E_{PAH}$ and $E_{IN}$ ($E_{PAH}$ being reduced to a greater extent than $E_{IN}$) during normal or nearly normal renal blood flow, as calculated from the PAH clearance and $E_{PAH}$. ($C_{PAH}/E_{PAH}$).

Reduction in the renal oxygen A-V difference during normal or nearly normal renal blood flow would be good evidence of a shunt because in few conditions would it be expected that the oxygen consumption of the kidney would be decreased except as there was some reduction in renal blood flow. A difficulty here is that the renal oxygen A-V difference is normally so small in man (0.5 to 2.0 volumes/100 cc.) that reductions in this value might not exceed the compounded analytic errors and would be difficult to interpret. If arterialization of the blood occurred as described in the rabbit, however, the oxygen A-V difference should decrease to a value close to zero and this should scarcely escape detection.

Thus the best evidence of what we may call a Trueta by-pass would be simultaneous reduction in $E_{PAH}$, $E_{IN}$ and renal oxygen A-V difference at a time when the total renal blood flow was maintained or but slightly reduced. When during marked renal ischemia there exists the possibility of impairment of tubular excretion and reduction in filtration pressure, the only acceptable evidence for a shunt would be reduction of the oxygen A-V difference to practically zero, i.e., complete arterialization of the renal venous blood. The evidences for the demonstration of such shunt are all technically available in the human kidney.

## NORMAL OR NEARLY NORMAL RENAL BLOOD FLOW

*The Normal Kidney.* The evidence is wholly against the existence of an appreciable circulation through inert juxtamedullary pathways in the normal human kidney. We have determined $E_{PAH}$ in thirty-five normal subjects (Table 1) varying in age from twenty to sixty-eight years; the average value is 0.92, with a range of 0.88 to 0.97. This figure is in agreement with other studies on normal subjects.[21–25] In effect, 90 per cent or more of the blood entering the renal artery is completely cleared of PAH before it emerges in the renal vein. Some of this blood perfuses the capsule and perirenal fat and non-excretory tissues in the calices and pelvis; this inert tissue must account for a considerable fraction of the uncleared blood, leaving a negligible or zero volume to be accounted for as passing through the juxtamedullary glomeruli. Since the juxtamedullary glomeruli must, by all accounts, receive a considerable fraction of the total circulation, it follows that they do not have any unique significance in respect to tubular excretion.

*Senescence.* Trueta and his colleagues suggest that in elderly normal persons protracted or repeated medullary diversion leads to canalization of glomeruli, with a consequent reduction of filtering surface and in the filtration rate. Davies and Shock[26] showed that the filtration rate decreases with advancing age, but tubular tissue also degenerates, as shown by a progressive reduction in $Tm_D$ with no significant change in the $C_{IN}/Tm_D$ ratio. The effective renal plasma flow also suffers progressive decrease, the ratio $C_D/Tm_D$ decreasing significantly in the older age groups. The only interpretation which can be applied to these data is that with advancing age glomeruli and tubules undergo senescent degeneration in a closely parallel manner. $E_{IN}$ in our normal subjects, though not as constant as $E_{PAH}$ (range 0.11 to 0.31), shows no evident relationship to age. If aglomerular nephrons exist in the senescent kidney, they are not sufficiently numerous to make themselves evident in these functional studies.

TABLE I
RENAL EXTRACTION OF PAH AND INULIN IN NORMAL HUMAN SUBJECTS

| Subject | Age yr. | $E_{PAH}$ | $E_{IN}$ | Subject | Age yr. | $E_{PAH}$ | $E_{IN}$ |
|---|---|---|---|---|---|---|---|
| 1 | 20 | 0.95 | | 19 | 50 | 0.94 | |
| | | 0.95 | | | | 0.95 | |
| 2 | 31 | 0.90 | | 20 | 50 | 0.91 | 0.27 |
| | | 0.89 | | | | 0.90 | 0.25 |
| 3 | 35 | 0.96 | 0.20 | 21 | 50 | 0.92 | |
| | | 0.96 | 0.20 | | | 0.93 | |
| 4 | 36 | 0.94 | 0.15 | 22 | 51 | 0.90 | 0.20 |
| | | 0.95 | 0.22 | | | 0.92 | 0.23 |
| 5 | 36 | 0.89 | 0.22 | 23 | 51 | 0.95 | 0.24 |
| 6 | 36 | 0.91 | 0.23 | 24 | 53 | 0.91 | 0.12 |
| | | 0.94 | 0.25 | | | 0.93 | 0.11 |
| 7 | 37 | 0.94 | 0.23 | 25 | 55 | 0.95 | |
| | | 0.94 | 0.16 | | | 0.97 | |
| | | 0.93 | 0.15 | 26 | 55 | 0.92 | |
| 8 | 40 | 0.90 | | | | 0.97 | |
| 9 | 41 | 0.94 | | 27 | 59 | 0.95 | 0.25 |
| | | 0.91 | | | | 0.89 | 0.27 |
| 10 | 43 | 0.93 | 0.20 | 28 | 60 | 0.92 | |
| | | 0.90 | 0.23 | | | 0.92 | |
| 11 | 43 | 0.96 | | 29 | 60 | 0.90 | |
| 12 | 43 | 0.90 | 0.31 | 30 | 63 | 0.88 | 0.23 |
| | | 0.90 | 0.16 | | | 0.91 | 0.30 |
| 13 | 43 | 0.92 | 0.25 | 31 | 63 | 0.88 | |
| | | 0.92 | 0.12 | 32 | 65 | 0.89 | 0.16 |
| 14 | 44 | 0.95 | | | | 0.88 | 0.12 |
| 15 | 46 | 0.92 | | 33 | 66 | 0.91 | |
| | | 0.93 | | | | 0.91 | |
| 16 | 49 | 0.94 | | | | 0.91 | |
| | | 0.95 | | 34 | 67 | 0.90 | 0.21 |
| 17 | 49 | 0.89 | 0.20 | 35 | 68 | 0.92 | |
| | | 0.89 | 0.18 | | | 0.93 | |
| 18 | 49 | 0.90 | | | | | |
| | | 0.91 | | | | | |

*Antidiuresis.* The Oxford workers have suggested juxtamedullary diversion of blood, with diminished filtration and greater reabsorption of water in the thin segment, as a mechanism explaining the antidiuretic action of pitressin and of spontaneous changes in urine flow in the erect and supine positions, during emotional excitation and in other circumstances involving endogenous antidiuretic hormone secretion. The medullary diversion of blood as an explanation of antidiuresis was first proposed by Frey[27] in 1934 and in a somewhat modified form it has been developed by Fuchs and Popper[28] as a theory of water diuresis.

*Endogenous hormonal activity:* In eighteen normal subjects with urine flows ranging from 0.68 to 19.7 cc./min., and under extremely variable and at times rapidly changing states of hydration, $E_{PAH}$ remained within the range of 0.88 to 0.96. (Table II.) For example, in one instance (A. B.) while the urine flow fell from 13 to 2 cc./min., three successive extraction ratios were 0.93, 0.92 and 0.92. Renal oxygen A-V differences from thirteen of these subjects were within the normal range and showed no relationship to urine flow. These data demonstrate that during spontaneous changes in urine flow there is no diversion of blood through uncleared channels.

*Exogenous hormonal activity:* It is impossible to duplicate in human subjects the massive doses of pitressin which the Oxford workers administered to their animals, 0.20 to 20 pressor units/kg., equivalent on a body weight basis to 14,000 to 1,400,000 milliunits in man;* and indeed it is questionable

* Antidiuresis may be maintained in man by the administration of less than 50 milliunits per hour.

whether comparable amounts of antidiuretic hormone ever appear in the human or animal circulation.

Ten normal subjects have been examined during pitressin inhibition of water diuresis. (Table III.) Control observations were made during the period of water diuresis for at least two and usually more clearance periods of fifteen to forty-five minutes. Further observations were made thirty minutes after an intravenous injection of pitressin followed by a constant sustaining infusion of this hormone. In seven experiments physiologic doses of pitressin[29] were used (a priming dose of 50 milliunits and sustaining dose of 50 milliunits per hour). In three subjects (N. O., B. U. and M. I.) pharmacologic doses were employed: 2,000 to 5,000 milliunits. In these three subjects the pitressin caused marked facial and mucosal pallor and complaints of faintness, abdominal cramps and impending syncope. In all cases the effect of pitressin was manifested by a sudden reduction in urine flow and an increased U/P ratio of PAH.

TABLE II
RENAL EXTRACTION OF PAH AND A-V OXYGEN DIFFERENCE DURING VARYING STATES OF HYDRATION

| Subject | Age yr. | Urine Flow cc./min. | $E_{PAH}$ | Renal A-V Oxygen Difference cc./100 cc. |
|---|---|---|---|---|
| N. O. | 31 | 12.4 | 0.90 | |
| | | 14.1 | 0.89 | |
| G. A. | 35 | 9.0 | 0.96 | 1.8 |
| | | 10.2 | 0.96 | |
| F. I. | 36 | 9.7 | 0.94 | 1.7 |
| | | 6.4 | 0.95 | |
| K. I. | 36 | 7.2 | 0.91 | |
| | | 7.7 | 0.94 | |
| W. I. | 37 | 6.9 | 0.94 | 1.4 |
| | | 8.8 | 0.94 | |
| | | 8.4 | 0.93 | |
| A. B. | 38 | 13.0 | 0.93 | |
| | | 2.1 | 0.93 | |
| | | 2.0 | 0.92 | |
| P. A. | 43 | 1.3 | 0.90 | 0.4 |
| | | 1.6 | 0.90 | |
| W. H. | 43 | 2.5 | 0.92 | 0.6 |
| | | 1.6 | 0.92 | |
| F. L. | 46 | 6.6 | 0.91 | 0.94 |
| | | 10.8 | 0.93 | |
| C. L. | 50 | 1.4 | 0.91 | 1.9 |
| | | 0.8 | 0.90 | |
| C. H. | 50 | 7.6 | 0.92 | 1.6 |
| | | 19.7 | 0.93 | |
| P. O. | 51 | 2.0 | 0.90 | 0.96 |
| | | 3.1 | 0.92 | |
| R. O. | 59 | 1.7 | 0.93 | 2.1 |
| C. U. | 60 | 3.2 | 0.90 | |
| L. U. | 60 | 0.6 | 0.90 | |
| P. R. | 65 | 2.7 | 0.89 | 0.6 |
| | | 3.0 | 0.88 | |
| H. A. | 66 | 0.8 | 0.91 | 1.4 |
| | | 0.6 | 0.92 | |
| | | 0.9 | 0.91 | |
| W. A. | 67 | 4.3 | 0.90 | 1.9 |

Because of the possibility of rapid transient renal effects (with subsequent autonomic adjustment of the renal circulation), particular attention was given to the immediate effects of the hormone in three subjects (B. U., M. I. and L. A.). Extraction ratios were obtained two minutes, nine and one-half and two minutes, respectively, after the injection of pitressin, during which time all three subjects were visibly pallid. Renal oxygen A-V differences were obtained fourteen minutes, eight and one minute after pitressin while clearances were continued throughout the entire period of equilibration.

The PAH and inulin clearances showed no significant or constant changes following pitressin; $E_{PAH}$ remained constant, varying in either direction by 1 to 3 per cent in all subjects except M. I. in whom this value decreased by 5 per cent, scarcely a significant drop; the renal oxygen A-V difference, however, coincidently increased in this subject. Renal oxygen A-V differences and renal extraction of oxygen ($E_{O_2}$) increased in six subjects and decreased in three, these changes occurring independently of minor variations in clearances or extraction ratios. Extraction ratios of inulin were observed in only a few of these subjects because of the large technical error in this measurement. An analytic error of 3 or 4 per cent in the inulin analysis will cause wide variations in the calculation of $E_{IN}$ in which two fairly close blood levels are being compared. But in no case was there a large change in this value.

Our observations on the effects of pitressin in man are in agreement with those of

Corcoran and Page[3] in dogs which received large amounts of pitressin over protracted periods and reveal no evidence of juxtamedullary diversion during spontaneous changes in urine flow or after the injection of pitressin.

Dog experiments were inconclusive but these authors conclude that large renal shunts cannot be elicited in man by physiologic doses or in dogs by larger doses of these drugs. In two unpublished experiments conducted in this laboratory $E_{PAH}$

TABLE III

EFFECT OF INTRAVENOUS PITRESSIN ON RENAL EXTRACTION RATIOS AND A-V OXYGEN DIFFERENCE

| Subject | Age Yr. | Dose* Milliunits | Urine Flow† cc./min. | | $E_{PAH}$† | | $E_{IN}$† | | Renal A-V Oxygen Difference—cc./100 cc. | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Before | After | Before | After | Before | After | Before | After |
| W. I. | 20 | 50 | 8.0 | 0.7 | 0.94 | 0.94 | 0.18 | 0.19 | 1.41 | 1.29 |
| D. E. | 41 | 50 | | | 0.91 | 0.91 | | | 1.21 | 2.04 |
| P. O. | 51 | 50 | | | 0.91 | 0.90 | 0.21 | 0.16 | 0.86 | 0.65 |
| C. L. | 50 | 50 | | | 0.91 | 0.89 | 0.27 | 0.24 | 1.94 | 2.50 |
| M. A. | 50 | 50 | 15.7 | 2.7 | 0.84 | 0.85 | 0.16 | 0.20 | 1.14 | 2.24 |
| H. A. | 44 | 50 | 7.0 | 0.9 | 0.95 | 0.96 | | | 1.50 | 2.20 |
| L. A. | | 50 | | | 0.92 | 0.93 | | | 1.65 | 0.66 |
| M. I. | 63 | 2000 | 5.7 | 1.8 | 0.89 | 0.85 | 0.26 | 0.23 | 1.22 | 1.40 |
| B. U. | 51 | 2500 | 6.7 | 1.5 | 0.95 | 0.92 | 0.24 | 0.30 | 2.81 | 4.52 |
| N. O. | 31 | 5000 | 13.9 | 0.8 | 0.90 | 0.91 | | | | |

* Figures represent priming and sustaining dose in milliunits per hour.
† All figures represent the average of 2 to 5 values.

*Adrenalin and Histamine.* The Oxford workers elicited juxtamedullary diversion in the rabbit by the intravenous administration of adrenalin in doses of 0.1 to 0.17 mg./kg., and they suggested that the reduction in renal blood flow produced by the administration of smaller doses in man (0.5 mg. subcutaneously and 0.5 mg. intramuscularly)[31,32] is in part attributable to this phenomenon. But Reubi and Schroeder[23] report that adrenalin (0.5 to 0.8 mg.) administered subcutaneously to man produced no significant change in $E_{PAH}$, the greatest decrease being 11.4 per cent. The renal oxygen A-V difference was increased in two subjects and decreased in three, but the latter did not decrease simultaneously with any fall in $E_{PAH}$. Similar results were obtained by Reubi and Futcher[33] with subcutaneous histamine (0.5 mg.) in three subjects, no changes occurring in $E_{PAH}$ or $E_{IN}$. Observations were not made on the oxygen A-V difference in these subjects. has remained constant after the administration of 1.0 mg. of adrenalin (0.5 mg. subcutaneously and 0.5 mg. intramuscularly) despite a marked reduction in renal blood flow, confirming the observations of the St. Louis group.

*Arterial-Venous Anastomoses.* Cargill[34] has attributed the decrease in $E_{PAH}$ which follows the administration of serum albumin to man to diversion of blood through the juxtamedullary circulation. There is concomitantly a marked increase in renal plasma flow and a decrease in the corrected filtration fraction but this is hemodynamically possible without positing juxtamedullary diversion. It is important to note that in every case the filtration rate increased, the average increase being 7 per cent, a fact which argues against diversion of blood from the cortex by any route.

Michie, Gimbel and Riegel[35] believe that the administration of albumin opens arterial-venous anastomoses without divert-

ing blood away from the glomeruli, since they observed no change in filtration rate, PAH clearance, $Tm_{PAH}$ or $Tm_G$ during the hyperemia and at a time when $E_{PAH}$ was reduced. Barker, Clark, Crosley and Cummins[36] confirm these observations with respect to filtration rate, PAH clearance, $E_{PAH}$ and $Tm_{PAH}$ and concur in the conclusion reached by Michie et al. They find that the renal oxygen A-V difference decreases by 30 to 40 per cent as the total renal blood flow increases, a fact which would be consonant with this interpretation.

It is possibly by such channels that the glass spheres of Simkin, Bergman, Silver and Prinzmetal[37] pass from the arterial to the venous side of the renal circulation. Such non-excretory channels appear, however, to be of slight functional importance, since they permit by-passing of at most a few per cent of the blood in the normal human kidney and there is no evidence of their activity in any of the pharmacologic or clinical circumstances cited in this paper.

### RENAL ISCHEMIA

As argued above, during renal ischemia the only acceptable evidence for a Trueta shunt would be almost complete arterialization of the renal venous blood, since $E_{PAH}$ and $E_{IN}$ might be reduced by diffuse renal anoxia with impairment of tubular excretion and simultaneous reduction of filtration pressure. However, the presence of normal or elevated values of $E_{PAH}$ and $E_{IN}$ would constitute positive evidence against a shunt.

*Essential Hypertension.* The Oxford investigators have advanced the hypothesis that diversion of blood through the juxtamedullary circulation plays a role in the genesis of essential hypertension by rendering the renal cortex ischemic, thereby initiating or permitting the formation of a renal pressor substance.

Bradley[21] reports an average $E_{PAH}$ of 0.92 (0.854 to 1.00) on twelve patients with essential hypertension, although the PAH clearance was reduced in some instances by as much as 50 per cent, showing the presence of marked renal ischemia. $E_{PAH}$ was significantly decreased in only two additional subjects both of whom were uremic. Reubi and Schroeder[23] report an average $E_{PAH}$ of 0.855 (0.698 to 0.950) in eight subjects and Cargill[24] an average of 0.895 (range 0.87 to 0.91) in four subjects with uncomplicated hypertensive disease. As Bradley and Cargill emphasize, only in the advanced stages of the disease is $E_{PAH}$ reduced and here the reduction may be anticipated because of destruction of proximal tubule tissue, as shown by reduction in $Tm_{PAH}$. The fact that the filtration fraction is generally elevated in hypertensive disease requires, in the face of a normal value for $E_{PAH}$, that $E_{IN}$ be normal or slightly elevated; whereas in this disease the Oxford workers found the largest numbers of canalized glomeruli, which should reduce $E_{IN}$ and filtration fraction. The renal oxygen A-V difference in Cargill's four subjects was above his control average of 1.42 cc./100 cc. in two and below it in two, averaging 1.29, but the data present no evidence of arterialization of renal venous blood.

These data show that there is no increase in uncleared blood in essential hypertension, as would be required by a Trueta by-pass and there is no warrant for the suggestion that such a shunt is in any way concerned in the development of this disease.

*Congestive Heart Failure.* Although the present information on renal hemodynamics in chronic congestive heart failure was not available at the time the Oxford monograph was prepared, the greatly reduced renal blood flow and filtration rate in this condition would seem to make it a suitable circumstance for a by-pass to operate, if one exists. Mokotoff and his co-workers[25] have examined twelve subjects with right-sided heart failure and found values of $E_{PAH}$ of 0.88 to 0.91, identical with their control series. Four subjects studied in this laboratory give similar results (range 0.88 to 0.96). Merrill[38] reports an average $E_{PAH}$ of 0.895 (range 0.835 to 0.930) in seven cases of congestive failure uncomplicated by renal disease and Edelman and his colleagues[39] report an average $E_{PAH}$ of 0.90 (range 0.88

to 0.91) in ten subjects in congestive failure. In nine subjects with congestive failure we have found a definite increase in renal oxygen A-V difference (average 2.8 cc/100 cc.) as compared with our normal average value of 1.4 (thirty-six subjects).

As in essential hypertension $E_{IN}$ should be especially significant in this condition, a chronic disorder in which one might expect to find a large proportion of degenerate glomeruli. In the nine cases studied here and in all those reported by Mokotoff and his co-workers, $E_{IN}$ was seldom significantly below normal (0.19) and in most cases was somewhat elevated.

*Shock and Anuria.* It was the study of the crush syndrome during World War II that led the Oxford group into its detailed investigations of the renal circulation. Basing their conclusions on their own evidence and on their interpretation of the work of others, they conceive that juxtamedullary diversion underlies the anuria of traumatic and hemorrhagic shock, transfusion reactions, septic abortion, nephrotoxins (sulfonamides), blackwater fever and cholera.

No data on extraction ratios in man during or following shock are as yet available. Lauson, Bradley and Cournand[40] in their study of human renal function during acute shock inferred that except in the most severe cases (in which the effective renal blood flow was reduced to less than 100 cc./min.) $E_{PAH}$ was probably normal. The inference was unsupported by actual measurements but the similarity in respect to circulatory inadequacy and in the degree of reduction of cardiac output and renal clearances in shock and in subjects with congestive heart failure may be held to support the inference.

More importantly, Phillips, Dole, Hamilton, Emerson, Archibald and Van Slyke[41] found that in acute hemorrhagic and traumatic shock in the dog the kidneys continue to extract PAH with the same degree of completeness ($E_{PAH} = 0.87$) until shock is so severe that the renal blood flow is decreased to below 3 per cent of normal, a condition reached only after shock was maintained for several hours by repeated hemorrhage or trauma. Qualitatively similar observations have been made by Corcoran and Page.[42] The fact that the renal oxygen A-V difference did not increase until the very late stages of shock[43] in contrast to the immediate increase in extraction by the body as a whole might be interpreted as indicative of diversion of blood through channels not presented to the renal parenchyma for clearance; but the injection of dyes (India ink, Evans blue or trypan blue) into the renal artery of three dogs during the terminal stage of shock revealed that the kidney was uniformly perfused. Histologic studies of some of these kidneys have revealed no instance of selective cortical ischemia.[44] Van Slyke,[45] in reviewing the experiments of the Rockefeller group on shock in dogs, rejects the diversion hypothesis, chiefly because the renal blood flow is decreased rather than increased, as would be expected if free vascular channels were opened in the medulla. Maluf,[15] in studies on dehydrated dogs infused with hemoglobin, found equal and normal injection of the cortex and medulla with India ink following anuria or marked diminution of clearances. In reversible shock in dogs he found a diminished injection of the entire kidney, with more dye in the cortex than in the medulla.

*Anuria.* In four subjects recovering from oliguria caused by inhalation carbon tetrachloride poisoning, Sirota[46] has demonstrated great reduction in renal blood flow, filtration rate, $E_{PAH}$ and $E_{IN}$ during the early stages of spontaneous diuresis, with a gradual return of renal clearances toward normal during a period of 100 to 200 days after the onset of the oliguria. He attributes the decreased extraction of PAH and inulin to tubular damage caused by anoxia, which he believes causes increased tubular permeability and unselective reabsorption of the glomerular filtrate.

Breed and Maxwell[47] have made observations during oliguria which persisted for 8 days in a subject suffering a post-transfusion reaction and found $E_{PAH}$ to be reduced to

0.06, with a renal oxygen A-V difference of 2.5 cc./100 cc. Clearance studies at this time were so low as to be uninterpretable. Six days after the onset of diuresis, $Tm_{PAH}$ was zero, and all clearances were at a very low level, indicating tubular reabsorption of all substances in the glomerular filtrate. Examination 102 days after the onset of oliguria showed $E_{PAH}$ to be 0.90 and the renal oxygen A-V difference of 1.6 cc./100 cc., both within normal limits, although at this time the PAH and inulin clearances were less than 50 per cent of average normal values. These last observations are consonant with non-perfusion of large and presumably damaged areas in the kidney, such tissue as is perfused functioning normally.

Clark, Barker and Crosley[48] have reported on a patient anuric for eight days following a transfusion reaction. Extraction ratios of all substances measured were very low, indicating almost complete cessation of renal function. However, the renal oxygen A-V difference was 1.53 cc./100 cc., this normal value indicating perfusion of metabolizing tissue rather than the operation of a by-pass.

The evidence at present is not conclusive but it argues against the diversion of blood in man in oliguria of traumatic or toxic origin because (1) the renal blood flow is consistently reduced, whereas if juxtamedullary diversion occurred this would not be the case; (2) the renal oxygen A-V difference is increased, rather than decreased; (3) $E_{PAH}$ recovers ahead of the PAH clearance, indicating that such blood as does perfuse the recovering kidney is cleared in the normal manner and (4) the absence of morphologic evidence of local cortical ischemia in kidneys from experimental or clinical cases. At the moment the more probable explanation appears to be that protracted anoxia or chemical injury destroys the integrity of the renal tubules leading, to a greater or lesser extent, to reabsorption of all constituents in the tubular urine. Recovery of circulation and tubular function proceeds *pari passu* so that at intermediate stages of recovery the blood is cleared in a normal manner.

## COMMENTS

In brief, the positive evidence excludes the diversion of any appreciable quantity of blood through uncleared channels in the normal human kidney, in senescence, antidiuresis induced endogenously or by the administration of pitressin, during the action of adrenalin, histamine and renal hyperemia produced by pyrogen or albumin, essential hypertension and cardiac failure in man, and in traumatic and hemorrhagic shock in the dog. There is no positive evidence of such diversion (and the data can be otherwise interpreted) in such oliguric states as have been examined in man.

The important points at issue, then, are: (1) Does the juxtamedullary circulation constitute a unique circuit through which blood may be diverted from the arterial to the venous system without exposure to the renal parenchyma for clearance in quantitatively the same manner as blood perfusing the cortical glomeruli? (2) Does preferential diversion through the juxtamedullary circuit ever occur in man? In respect to (1), in the light of the anatomy reviewed previously, we are not inclined to believe that the juxtamedullary circulation differs from the cortical circulation as much as the Oxford workers imply. The relative number of glomeruli in man which supply the *vasa recta* is probably as large (20 per cent) as they indicate, and accepting this estimate, and accepting the premise that these glomeruli and the dependent *vasa recta* are normally perfused with a proportional quantity of blood, one must conclude from the demonstrated values of $E_{PAH}(= 0.92)$ that this blood is presented to proximal tissue for clearance.

The descending straight limb of Henle's loop from the juxtamedullary glomeruli penetrates the "outer zone" of the medulla where it is surrounded by or admixed with *vasa recta;* only in the inner band of the outer zone and the inner zone of the medulla is the medulla composed exclusively of thin segments. Trueta and his colleagues treat these thick-walled tubules as part of the "loop of Henle" (descending limb),

which in a historical and anatomic sense is correct but functionally is misleading in that it implies functional equivalence with the thin limb. These thick-walled tubules are anatomically similar to the proximal convoluted tubules and must be considered functionally as proximal tubular tissue. Thus even if the efferent blood from the juxtamedullary glomeruli is restricted wholly to the *vasa recta* (*i.e.*, if the *vasa recta* have no capillary offshoots), this proximal tissue in the descending limb of the loop of Henle could extract PAH from this blood in a normal manner, for it is in intimate relation with both the descending and ascending portions of the *vasa recta*. On the other hand, the thin limb terminates in a thick ascending limb which may be of considerable length within the medulla; if this segment is functionally identical with distal convoluted tubular tissue, and one may presume that it is, it could perform the reabsorptive functions usually ascribed to the other. In brief, the vascular-tubular relations in the outer medulla are such as to permit essentially the same clearance functions for the juxtamedullary glomeruli as for the cortical glomeruli.

It is also possible that the circulation of interstitial fluid, which is believed to move from the medulla toward the cortex, carries dialysate from the vasa recta back into the juxtamedullary region to such an extent as to nullify any local anatomic distribution of tubular tissue. Of these two possibilities, we consider the first of greater probability and importance.

Being led by the available evidence to a negative answer to (1), it follows that exclusive perfusion of the juxtamedullary glomeruli may occur under certain conditions but it will not be revealed by any criteria which involve glomerular or tubular function. Such diversion would have no consequences other than the production of cortical ischemia; its physiologic significance would be limited to this fact.

There remains, then, the evidence that in the rabbit (and perhaps to some extent in other mammals) the juxtamedullary glomeruli may continue under perfusion when the cortical nephrons are devoid of blood. Evidence to be reviewed elsewhere[49] indicates that the fetal development of the human kidney is not paralleled in all mammals. Development of the glomeruli proceeds from the juxtamedullary region toward the capsule, with progressive elongation of both proximal and distal tubules; but more importantly, the human fetus appears to have its full complement of well differentiated glomeruli at birth, whereas in the rat the number of such fully differentiated glomeruli approximately doubles between birth and maturity. One may anticipate that late into gestation in the rat much of the fetal circulation is through the juxtamedullary circulation; there is no obvious need for extensive vasoconstriction in the fetal renal circulation and it may be that sympathetic fibers establish poor connection with these juxtamedullary glomeruli, whereas vasomotor connections are richer to the glomeruli in the neogenic zone which undergoes differentiation after birth. In the human fetus, however, carrying its full complement of glomeruli at birth, sympathetic connections may have been established more uniformly throughout the juxtamedullary and the cortical zones. No data are available on the rabbit but on the presumption that this species may resemble the rat, differences in the effectiveness of vasomotor innervation may be attributable to species differences in the sequence of maturation of the juxtamedullary and cortical zones. In this view the juxtamedullary circulation in the rabbit and perhaps other mammals may represent a vascular area refractory to neurogenic vasoconstriction but otherwise having no unique functional significance.

## SUMMARY AND CONCLUSIONS

On the basis of data in the literature and experimental studies presented here, an attempt has been made to assess the functional significance of the renal juxtamedullary circulation in man.

The positive evidence from clearance and extraction ratio data and histologic studies

excludes the diversion of any appreciable quantity of blood through uncleared channels in the normal human kidney, in senescence, antidiuresis induced endogenously or by the administration of pitressin, during the action of adrenalin, histamine and renal hyperemia produced by pyrogen or albumin, and in essential hypertension and chronic congestive cardiac failure in man; and in traumatic and hemorrhagic shock in the dog. There is no positive evidence of such diversion in such oliguric states (traumatic and hemorrhagic shock, transfusion reaction and carbon tetrachloride intoxication) as have been examined in man.

The thick descending and ascending straight limbs of Henle's loop, which are cytologically similar to convoluted proximal and distal tubular tissue, are in intimate contact with the *vasa recta* in the outer zone of the medulla and could effect essentially the same clearance functions for the juxtamedullary glomeruli as the convoluted tubules do for the cortical glomeruli. It is possible that circulation of interstitial fluid from the medulla toward the cortex carries dialysate from the *vasa recta* into contact with cortical tissue and thus nullifies the functional importance of the anatomic peculiarities of the juxtamedullary circulation.

The juxtamedullary circulation in man has no unique functional significance as far as can be ascertained at the present time.

Experimental perfusion of the juxtamedullary circuit during cortical ischemia has been partially confirmed in the rabbit but has failed of confirmation in the dog, as in man. It is suggested that this circumstance may reflect a species difference in the fetal development of the kidney and the degree of renal maturity at birth.

## REFERENCES


1. Trueta, J., Barclay, A. E., Daniel, P. M., Franklin, K. J. and Prichard, M. M. L. Studies of the Renal Circulation. Springfield, Ill., 1947. C. C Thomas.
2. Peter, K. Untersuchungen über Bau und Entwickelung der Niere. Jena, 1927. Gustav Fischer.
3. Spanner, R. Über Gefässkurzschlüsse in der Niere. *Verhandl. d. anat. Gesellsch.*, 45: 81, 1938.
4. Montague, F. E. and Wilson, F. L., Jr. Effect of epinephrine and shock on sodium para-aminohippurate extraction by the rabbit kidney. *Am. J. Physiol.*, 159: 581, 1949.
5. Cort, J. H. and Barron, D. H. Neural control of the renal shunt. *Federation Proc.*, 7: 23, 1948.
6. Arcadi, J. A. and Farman, F. Experimental studies and clinical aspects of the renal circulation. *J. Urol.*, 62: 756, 1949.
7. Palmlöv, A. Some observations on the Trueta renal vascular shunt. *Scandinav. J. Clin. Lab. Invest.*, 1: 308, 1949.
8. Moyer, J. H., Conn, H., Markeley, K. and Schmidt, C. F. Hemodynamics of renal circulation. *Am. J. Physiol.*, 159: 582, 1949.
9. Goodwin, W. E., Sloan, R. D. and Scott, W. W. The "Trueta" renal vascular "shunt." an experimental demonstration of neurovascular control of the renal circulation in the rabbit, cat, dog and man. *J. Urol.*, 61: 1010, 1949.
10. Black, D. A. K. and Saunders, M. G. Experimental observations on renal blood flow. *Lancet*, 256: 733, 1949.
11. Kahn, J. R., Skeggs, L. T. and Shumway, N. P. Studies of the renal circulation. *Circulation*, 1: 445, 1950.
12. Study, R. S. and Shipley, R. E. Effects of renal artery-nerve stimulation on renal blood flow measured directly, and by clearance and extraction of diodrast. *Am. J. Physiol.*, 159: 592, 1949.
13. Houck, C. R. Possible renal vascular shunt in dogs during intravenous epinephrine. *Federation Proc.*, 9: 63, 1950.
14. Draper, W. B. and Whitehead, R. W. The phenomenon of diffusion respiration. *Anesth. & Analg.*, 28: 307, 1949.
15. Maluf, N. S. R. Factors inducing renal shut-down from lysed erythrocytes: an experimental study. *Ann. Surg.*, 130: 49, 1949.
16. Marshall, E. K., Jr. The secretion of urine. *Physiol. Rev.*, 6: 440, 1926.
17. Chambers, R. and Kempton, R. T. Indications of function of the chick mesonephros in tissue culture with phenol red. *J. Cell. & Comp. Physiol.*, 3: 131, 1933.
18. Cameron, G. and Chambers, R. Direct evidence of function in kidney of an early human fetus. *Am. J. Physiol.*, 123: 482, 1938.
19. Forster, R. P. Personal communication.
20. Wesson, L. G., Jr., Anslow, W. P., Jr. and Smith, H. W. The excretion of strong electrolytes. *Bull. New York Acad. Med.*, 24: 586, 1948.
21. Bradley, S. E. The validity of the clearance technique in the measurement of renal blood flow in normal man and in patients with essential hypertension. Josiah Macy, Jr. Foundation Conf., Tr. First Conf., 119, April 24-25, 1947.
22. Bradley, S. E. and Halperin, M. H. Renal oxygen consumption in man during abdominal compression. *J. Clin. Investigation*, 27: 635, 1948.
23. Reubi, F. C. and Schroeder, H. A. Can vascular shunting be induced in the kidney by vasoactive drugs? *J. Clin. Investigation*, 28: 114, 1949.
24. Cargill, W. H. The measurement of glomerular and tubular plasma flow in the normal and

diseased human kidney. *J. Clin. Investigation*, 28: 533, 1949.
25. Mokotoff, R. Personal communication.
26. Davies, D. F. and Shock, N. W. Age changes in glomerular filtration rate, effective renal plasma flow and tubular excretory capacity in adult males; (in preparation).
27. Frey, E. Der Mechanismus der Harneindickung und der Harnverdünnung. *Arch. f. exper. Path. u. Pharmakol.*, 177: 134, 1934.
28. Fuchs, F. and Popper. The Flow of Water through the Kidney. New York, 1944. Manhattan Printing Company.
29. Lauson, H. D., Eder, H. A., Chinard, F. P., Cotzias, G. C. and Greif, R. L. Estimation of the rate of antidiuretic hormone secretion in normal man. *Federation Proc.*, 7: 69, 1948.
30. Corcoran, A. C. and Page, I. H. The effects of renin, pitressin and atropine on renal blood flow and clearance. *Am. J. Physiol.*, 126: 354, 1939.
31. Smith, H. W. Lectures on the Kidney. Lawrence, Kan., 1943. University Extension Division, University of Kansas.
32. Chasis, H., Ranges, H. A., Goldring, W. and Smith, H. W. The control of renal blood flow and glomerular filtration in normal man. *J. Clin. Investigation*, 17: 683, 1938.
33. Reubi, F. C. and Futcher, P. H. The effects of histamine on renal function in hypertensive and normotensive subjects. *J. Clin. Investigation*, 28: 440, 1949.
34. Cargill, W. H. Effect of the intravenous administration of human serum albumin on renal function. *Proc. Soc. Exper. Biol. & Med.*, 68: 189, 1948.
35. Michie, A. J., Gimbel, N. S. and Riegel, C. Personal communication.
36. Barker, H. G., Clark, J. K., Crosley, A. P., Jr. and Cummins, A. J. The effect of salt poor human albumin on renal oxygen consumption in man. *Am. J. M. Sc.*, 218: 715, 1949.
37. Simkin, B., Hergman, H. C., Silver, H. and Prinzmetal, M. Renal arteriovenous anastomoses in rabbits, dogs and human subjects. *Arch. Int. Med.*, 81: 115, 1948.
38. Merrill, A. J. Edema and decreased renal blood flow in patients with chronic congestive heart failure: evidence of "forward failure" as the primary cause of edema. *J. Clin. Investigation*, 25: 389, 1946.
39. Edelman, L. S. Personal communication.
40. Lauson, H. D., Bradley, S. E. and Cournand, A. The renal circulation in shock. *J. Clin. Investigation*, 23: 381, 1944.
41. Phillips, R. A., Dole, V. P., Hamilton, P. B., Emerson, K., Jr., Archibald, R. M. and van Slyke, D. D. Effects of acute hemorrhagic and traumatic shock on renal function of dogs. *Am. J. Physiol.*, 145: 314, 1946.
42. Corcoran, A. C. and Page, I. H. Effects of hypotension due to hemorrhage and of blood transfusion on renal function in dogs. *J. Exper. Med.*, 78: 205, 1943.
43. Dole, V. P., Emerson, K., Jr., Phillips, R. A., Hamilton, P. and van Slyke, D. D. The renal extraction of oxygen in experimental shock. *Am. J. Physiol.*, 145: 337, 1946.
44. Oliver, J. Personal communication.
45. van Slyke, D. D. The effects of shock on the kidney. *Ann. Int. Med.*, 28: 701, 1948.
46. Sirota, J. H. Carbon tetrachloride poisoning in man. I. The mechanisms of renal failure and recovery. *J. Clin. Investigation*, 28: 1412, 1949.
47. Breed, E. S. and Maxwell, M. H. Renal studies in a patient with transfusion anuria; (in preparation).
48. Clark, J. K., Barker, H. G. and Crosley, A. P., Jr. Evidence against renal vascular shunts in a case of lower nephron nephrosis; (in press).
49. Smith, H. W. The Kidney: Structure and Function in Health and Disease. Oxford University Press; (in press).

# Renal Physiology in Infancy*

R. A. McCance, F.R.S.
*Cambridge, England*

In nature, animals are so perfectly adapted to their environments that it is difficult to appreciate the little essentials of physiology that go to make that adaptation a success. Much of our knowledge of physiology has been derived from a study of the animal under stress—that is to say, outside its normal environment. The stress may have been a change in temperature, humidity, barometric pressure or hydration, or one brought about by disease. Our knowledge of renal function in early life would certainly have been much less than it is today had our attention not been directed to it by the effects of disease and dehydration upon the well being and upon the serum chemistry of the infant. The problem has been directly and intensively studied only for the last ten or twelve years but observations were made before this time, and it is only necessary to add that it was the fundamental work of Gamble, Homer Smith and their associates in the 1930's which made it possible for our knowledge of the subject to develop in the way it has done since that time. The position was reviewed[39] after the Fifth International Congress in Paediatrics in New York. The subject has been treated rather differently in the present article, and a great deal of the older literature will be found in the previous review.

*Fluid Compartments of the Body.* It is helpful to begin any study of infant physiology by a consideration of the fluid compartments of the body. These are represented diagrammatically in Figure 1 which clearly shows that a premature infant has much more water in its body than the adult and that a greater part of this water is outside the cells.[24] The osmotic pressure of the fluid outside the cells and of the "free" fluid inside the cells has generally been assumed to be the same but data are accumulating which are not easy to fit in with this assumption.[53] In any case the salts outside the cells are predominantly sodium salts and those inside the cells potassium salts. The most obvious function of the kidney at all ages is the regulation of the constancy of the internal environment, i.e., the composition and, although not so directly, the volume of the extracellular fluid. A comparison of the serum chemistry of newborn infants and adults is therefore given in Table 1.[39] It will be seen that the serum of the infant differs in having less protein[16] and bicarbonate[20] but more chloride and phosphate, and that the concentrations of sodium and the osmotic pressures are the same. These similarities and differences are important and will be discussed later. The serum potassium is sometimes at adult levels but higher values have been reported by some observers in some otherwise normal infants.[43] The significance of this is obscure and a re-investigation of the matter may not substantiate this finding.[61] Average figures, therefore, for potassium have not been given in Table 1.

*Volume and Osmotic Pressure of the Urine in the "Newborn" Period.* The urine at this age well repays investigation and was carefully studied in the middle of the last century but has since received comparatively little attention. Some of the important features are shown in Figure 2 which is based principally upon the work of Daly et al.,[10] Heller,[28] McCance and von Finck,[41] Smith et al.,[59] Thomson[63] and papers cited in the previous review.

Important points to note are: (1) the

* From the Medical Research Council Department of Experimental Medicine, Cambridge, England.

extremely dilute urine passed before birth at a time when the mother, who must presumably be equally hydrated, would certainly be passing a much more concentrated one; (2) the small volumes of urine passed in the days following birth when the baby is getting practically nothing by mouth and (3) the more concentrated urine during this period of physiologic dehydration. The degree of concentration, however, never reaches that which would be achieved by an adult under comparable conditions, i.e., about 1,200 m.osmol./L. While the quantitative data given in Figure 2 are exclusively human, there is no doubt that these generalizations about the osmotic pressure of the urine before and soon after birth are true also of animals.[10,31,43] In an attempt to explain these observations Heller has studied the concentrations of antidiuretic hormones in the pituitaries of adult and newborn humans and rats.[29,32] The results calculated to body weight are shown graphically in Figure 3 and there can be no reasonable doubt of this difference due to age. It is evident that there are also striking species variations which may give a clue to some of the functional renal differences. In commenting on these results Heller made the interesting point that in spite of the small amount of hormone in the glands at birth, there should still be plenty there to produce a fully concentrated urine if it was released and if the kidney was responsive. The failure of the tubules to respond to the hormone is probably the crucial factor, for Heller has himself shown that babies seven to fourteen days old, taking their normal fluid diet and passing the dilute urine proper to that age, do not produce a highly concentrated urine in response to injected antidiuretic hormone, as adults would do if they were loaded with water and passing urine of comparably low osmotic pressure. Heller has never suggested that infants show no response to posterior pituitary hormone, and Barnett et al.[3] have shown that they respond when loaded with water, but the response was not compared with that of an adult and was probably less. Interest in the failure of normal infants to respond to pituitrin at this age has been enhanced by the discovery[11] that some infants never seem to acquire this ability, but it is still too early to say whether the pathologic lesion is really the maintenance of an infantile stage of development or not, or to explain it in terms of enzyme chemistry and cellular metabolism.

Even the solution of these problems would leave much to be explained for it has been shown repeatedly that as well as being unable to concentrate their urine like adults, newborn animals are also unable to dilute their urine as adults can in response to the usual stimulus of water by mouth. The most quantitative work has so far been done on animals. Puppies have been studied by Adolph,[1] newborn rats by Heller[30] and by McCance and Wilkinson,[43] and kittens by Tayler.[62] The basis of these observations has usually been the failure to

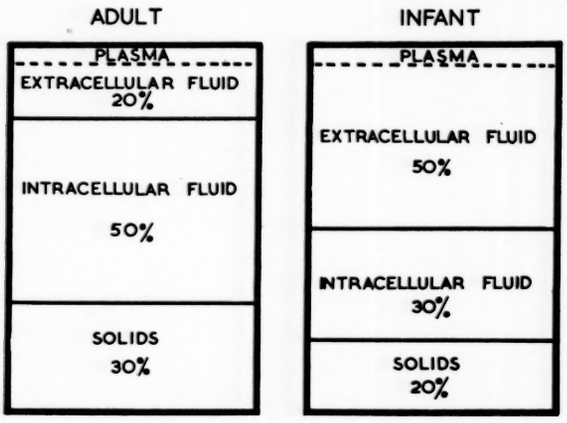



FIG. 1. A diagrammatic representation of the composition of the body of an adult and of a premature infant weighing about 2,000 gm.

TABLE I

SERUM CHEMISTRY OF ADULT AND NORMAL INFANT IN FIRST WEEK OF LIFE

| | Adult | Infant |
|---|---|---|
| Serum proteins gm./100 cc. | 7 | 5 |
| Serum Na mEq./L. | 140 | 140 |
| Serum Cl mEq./L. | 101 | 108 |
| Serum $HCO_3$ mEq./L. | 29 | 22 |
| Serum $PO_4$ mg./100 cc. | 2.5–4.5 | 5–8 |
| Osmotic pressure m.osmol./L. | 310 | 310 |

excrete the expected percentage of the water administered, but the osmotic pressure of the urine has also been investigated. Against this might appear to be set the observations of Barnett et al.[3] on premature infants aged three to twenty-eight days. These authors, however, approached the problem from a different angle. They were interested in glomerular filtration rates; and although they showed[5] that it was possible to obtain inulin U/P ratios as low as 3.9 and therefore high rates of urine flow, they did not produce the diuresis by giving water but by mannitol or saline infusions. They did not, moreover, compare the behaviour of adults under similar conditions. Their work, therefore, stands alone and involves no contradictions.

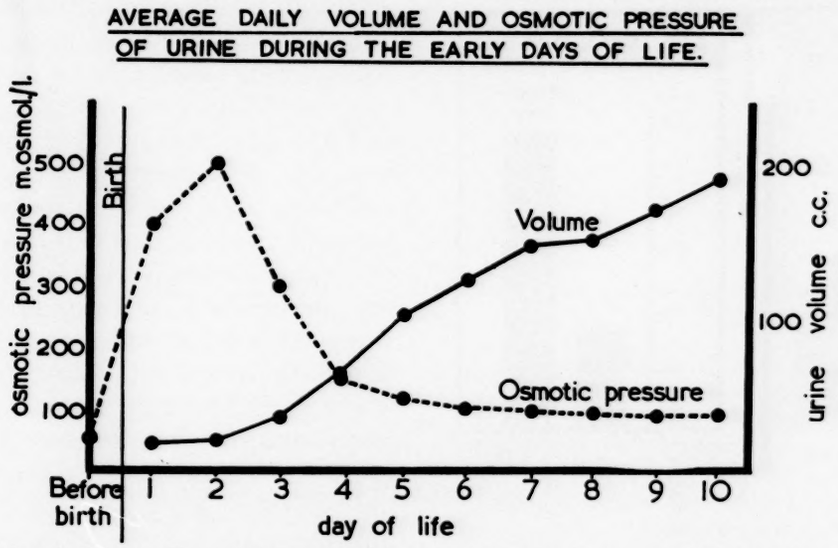



FIG. 2. The average daily urine volume and the osmotic pressure of the urine during the early days of life.

It is naturally important to discover the age at which the development of these various functions is complete. The first papers about animals contained some data about this but papers on human infants did not. Pratt, Bienvenu and Whyte[48] have now made a study of one aspect of this by limiting the fluid intake of five babies one to two months old. It would appear that these infants were able to excrete urines with osmotic pressures as high as 1,200 m.osmol./L. This is the adult level so that in this respect functional maturity would seem to be attained by healthy infants quite early in life, but so long as the inability to concentrate the urine persists the infant will lose more water through the kidney in excreting a given quantity of solutes than a healthy adult. This is represented diagrammatically in Figure 4. It is upon this aspect of renal function that Kerpel-Fronius[34,35] developed his elegant method of dehydrating puppies.

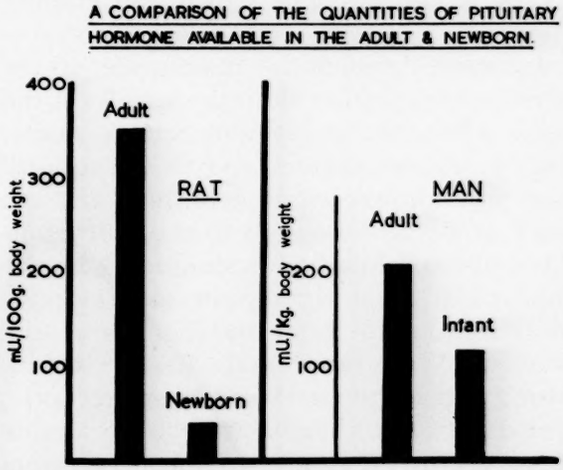



FIG. 3. A comparison of the quantities of pituitary hormone available in the adult and the newborn rat and human. The number of milli-units is expressed per 100 gm. body weight in the rat and per kg. body weight in the human.

*Glomerular Filtration Rate.* It was known when the subject was discussed in 1948 that

in spite of the low serum proteins in newborn infants (Table 1), the inulin and mannitol clearances were considerably lower than those of adults when compared on the basis of surface area. Since that time several sound investigations have been made to find out how quickly the glomerular filtration rates rise to the adult levels. Barnett et al.[4] studied the matter in premature babies up to three months of age and showed that on the whole the time which had elapsed since birth—in other words, the child's postnatal age—decided the magnitude of the filtration rate rather than the weight of the child when the investigation was made. This statement applies also to the tubular functions studied by these authors and the work as a whole suggests that the development of renal function is stimulated by the changes in renal circulation and responsibilities brought about by the loss of the placenta. West, Smith and Chasis,[70] Rubin, Bruck and Rapoport[56] and, more recently, Vesterdal and Tudvad[66,67] have made elaborate investigations of the maturation of renal function in childhood by the application of the standard clearance technics. All found considerable individual variations at all ages. West et al. concluded that glomerular filtration rates might reach functional maturity in from ten to twenty weeks in some infants; Vesterdal and Tudvad did not find any normal adult rates below four months; Rubin et al. none below six months, and many babies still had very low glomerular filtration rates at that age. (Fig. 5.) Some of these differences may be accounted for by technic, but they are large and it is clear that there is a wide scatter in the ages at which the glomerular filtration rate has been found to reach the adult level, and similar results must be expected in future investigations. Vesterdal and Tudvad[67] did not find that renal function was depressed by prematurity unless the birth weights were below 1,500 gm. Suranyi and Zimanyi[60] have used the endogenous creatinine clearance to follow the maturation of glomerular function. They concluded that development was slower than that suggested by Young and McCance[73] and they added the interesting point that it was affected by nutritional status.[17] In adults the endogenous creatinine clearance may have some value as an approximation to the glomerular filtration rate; but Brod and Sirota[9] found the creatinine clearances to be considerably lower than the mannitol clearances in infants and even in children as old as two years of age. This is perhaps enough to account for the Hungarian workers' conclusions, and it is to be hoped that they will be able to repeat their work with a more acceptable yard stick.

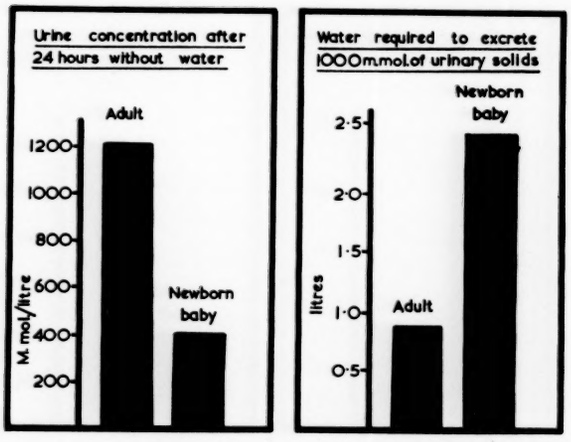



FIG. 4. A comparison in the adult and newborn of (1) the concentration of the urine after twenty-four hours without water and (2) the volume of water required to excrete 1,000 mM of urinary solids.

Two papers have recently been published on the effect of the hydration of the baby on the glomerular filtration rate. Barnett et al.[3] concluded that withholding fluids did not lower the inulin clearances of premature babies, but their diagram suggests that it did make a difference of perhaps 20 per cent. (Fig. 6.) Vesterdal and Tudvad[67] found that the administration of saline intravenously raised the glomerular filtration rate of some babies by 50 or even 100 per cent but did not alter it in others. The quantities given were not stated and water by mouth would have been a more interesting diuretic.[39] This subject is an important one and it is very much to be hoped that it will be further investigated under natural and induced conditions.

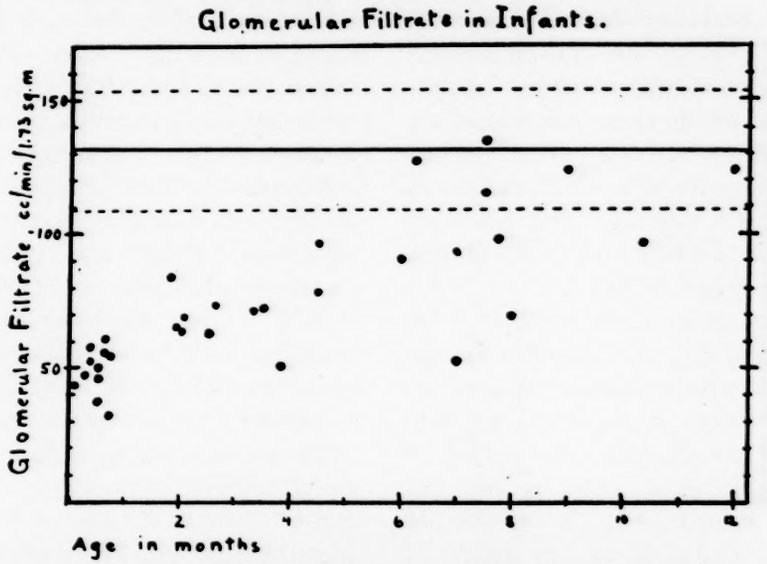



FIG. 5. Glomerular filtration rate in infants. Each dot represents the average value in an individual child. The horizontal line represents the mean value of the glomerular filtration rate of an adult with a surface area of 1.73 sq. m. The broken lines represent one standard deviation from this mean, as determined in adults. A very similar figure may be found in Vesterdal and Tudvad's article.[67] (From Rubin, Bruck and Rapoport.[56] Courtesy of *J. Clin. Investigation*, 28: 1144, 1949.)

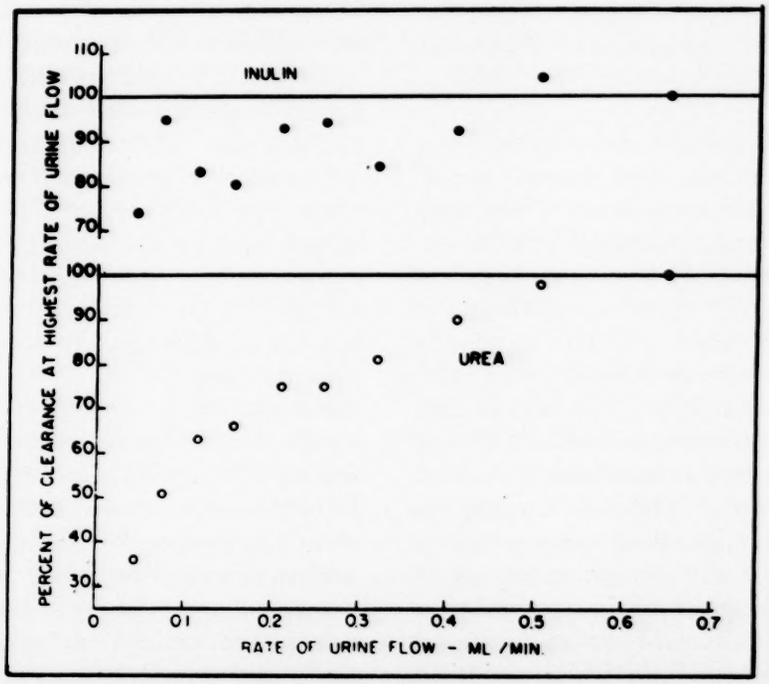



FIG. 6. Changes in inulin and urea clearances with changes in rate of urine flow in premature infants. These data were calculated from 100 periods during which inulin and urea clearances were measured simultaneously. Each point represents an average of ten periods. The clearances are expressed as a percentage of the average clearance at the highest average rate of urine flow observed (0.6 cc. per minute.) (From Barnett, Hare, McNamara and Hare.[3] Courtesy of *J. Clin. Investigation*, 27: 691, , 1948.)

Vesterdal and Tudvad[67] found that pain, caused for example by the subcutaneous injection of a large volume of fluid, might greatly reduce the glomerular filtration rate and also the clearances of p-amino hippurate. The filtration fractions did not as a rule change. These findings and all they imply seem an important addition to our knowledge of the infant kidney.

A paper has recently been published on water reabsorption by the tubules in infancy.[7] Endogenous creatinine was used as the measure of glomerular filtration rate and the authors' conclusions were (1) that the glomerular filtration rates were very low in newborn infants, (2) giving glucose raised the glomerular filtration rates of "healthy" infants aged two to eleven months but not of newborn or "atrophic" infants and (3) giving glucose increased the reabsorption of water. The evidence for some of these conclusions is not very convincing, and the uncertainty about the creatinine clearance as a measure of glomerular filtration rate has already been discussed. It is therefore difficult to assess the value of this paper.

*Urea Clearances and the Excretion of Other Nitrogenous Substances.* Our knowledge of the excretion of urea in infancy has been considerably extended within recent years. The clearances, already known to be small by adult standards,[39] have been studied in relation to the urine volumes and the glomerular filtration rates by Rubin et al.[56] and Barnett et al.[5] and a great deal of data may be found in their papers. It would appear that the urea clearances at high rates of urine flow in children during the first year of life are about 60 per cent of the glomerular filtration rates as measured by mannitol.[56] This relationship is similar to that found in adults and, as in adults, is subject to considerable individual variation. Rubin et al. found the individual ratios to range from 0.36 to 0.95 when the urine volumes exceeded 2 cc./1.73 sq.m./min. Barnett et al.'s[3] study of premature infants established that the urea clearance varied considerably with urine flow as it does in adults and that the urea/inulin clearance ratio rose with the urine flow. (Fig. 6.) They also observed that the urea clearances were subject to variations of unpredictable and sometimes considerable magnitude when the urine volume rapidly changed. In this respect, therefore, the kidney of the newborn infant seems to behave like the organ of the human adult[40] or the adult dog.[58] Sooner or later these studies and technics will have to be extended to sick children with azotemia. The paper of Doxiadis[18] shows up the gaps in our knowledge about renal function in such cases and emphasizes the need for further investigations. Thomson[64] has made a valuable contribution of a rather different type. He set out to study the urea clearances of infants under entirely natural conditions in the first few days of life. His periods of observation were often long and based upon spontaneous voidings, but he also made a series of one-hour collections by catheter. Urea was given by gavage to a number of the subjects. The mean minute volumes were small, 0.0682 to 0.089, but he as others found that the clearance varied with the urine flow. The average clearance of a group of nine babies with an average age of about fifty hours was only 1 cc./min. It was about 2 cc./min. after giving urea. These figures argue lower glomerular filtration rates than have so far been found in newborn infants,[39] for these urea clearances amount only to about 10 cc./1.73 sq.m./min. and at the lower minute volumes to much less. Thomson also made the interesting observation that in a number of the tests he was unable to withdraw any urine at all after a collection period of one to two hours and questioned seriously whether any had been formed. These observations under natural conditions of hydration show why the blood urea so often rises during the first few days of life.[42] Attention must also be drawn to the high concentrations of urinary urea which Thomson regularly observed after giving enough urea by mouth to raise the levels in the serum two to four times. This might have been predicted from previ-

ous data which was fully discussed in the last review.[39] It is a great pity that the inulin clearances were not measured by Thomson but no doubt this will be done. The low urea clearances in infancy explain why the serum urea is so easily doubled and more than doubled in premature infants by changing their diet from human milk to an enriched protein milk on which, incidentally, the infants may thrive.[55]

Barlow and McCance[2] made a study of the N partition of the urine in newborn infants. Although not strictly a study of renal function, some observations were made which have a bearing on it. The output of N was very small during the first days of life when compared with adults under similar conditions of starvation, and the urea formed a much smaller percentage of the total N than is usual in adults. Amino-N accounted for a higher percentage, and Vegter[65] has found considerable amounts of some amino acids in the urine of newborn premature babies. There is much to be found out about nitrogen metabolism at this age[26] and about the effect of dehydration upon it at all ages under one year.[18]

*Tubular Function.* The kidney function as a whole and the urine as we know it is the result of the integrated function of the glomeruli and the tubules. In adults this harmony may be disturbed by disease[49] and there is evidence now that in infants the tubules are in a state of not only functional immaturity but also that they have not yet taken up their adult relationship with glomerular function. Thus all the people who have studied the excretion of diodone or p-amino hippuric acid in infants[5,13,56,67] have found that these clearances are very low and furthermore that the so-called filtration fractions are high. This suggests that in the excretion of these substances tubular function is less developed than glomerular function.[67] (Fig. 7.) American papers contain a great deal of additional data about the excretion of p-amino hippuric acid at high plasma concentrations which confirms this conclusion, and it would appear that the ability of the tubules of premature infants to excrete penicillin is equally undeveloped, for Barnett et al.[6] found the penicillin/inulin clearance ratios to be of the order of 2.2 in such infants and to be about 4.2 in the older children. The scanty information which is available about

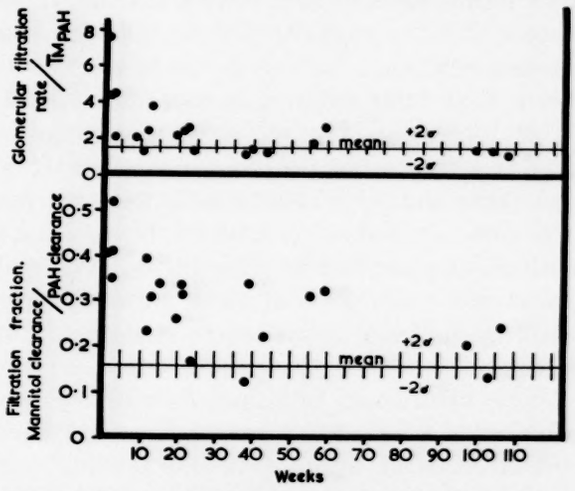



FIG. 7. Glomerular filtration rate/maximal excretion of p-amino hippurate (top) and filtration fraction (bottom) in infancy, the horizontal lines representing the mean standard adult value. A similar diagram for the filtration fraction containing more data is given by Vesterdal and Tudvad.[67] (Redrawn from West, Smith and Chasis.[70] Courtesy of *J. Pediat.*, 32: 10, 1948.)

the excretion of creatinine[9,13] suggests that the tubules of newborn infants have not yet developed an ability to excrete this substance. On the other hand, kittens fourteen to twenty-one days old have been found to have attained the glomerulotubular relationship characteristic of the adult cat[21] so far as the excretion of thiosulfate is concerned, so that by this age this species peculiarity seems to have become established.

Williamson and Hiatt[71] have made a study of tubular development in the rabbit by injecting phenolsulphonphthalein into fetal and young animals. The work seems to have been beautifully controlled but the relationship to surface area or to glomerular function was not studied. The authors found very low rates of excretion before birth and an increase of 100 times by the tenth day of life by which time the kidneys had increased in weight only by 10 to 20 times. This increased capacity to excrete dye may have been due to developments in the renal

blood supply or to increasing cellular activity, or to both. Baxter and Yoffey[8] have studied the way in which the tubule cells of newborn and developing rats take up trypan blue after the intravital injection of the dye. There are both anatomic and functional sides to this.[39] The authors have shown that many of the peripheral nephrons in the newborn rat are so undeveloped at birth that their tubules do not stain at all. This, however, may be a matter of functional glomerular development since it is probable that the tubule cells take up the dye from the lumen. The cells, however, do not take up the dye till they have developed a brush border so that these authors have done something to correlate structure and function.

The clearances of minerals and the excretion of acids and ammonia are functions which depend upon both glomerular and tubular function and a study of them has revealed further interesting differences between glomerular and tubular development at birth and for some little time afterward. These differences will be discussed when the clearances or excretions of the various substances are being considered.

*Sodium Chloride Clearances.* McCance and Young[44] originally showed that the sodium and chloride clearances in the first fourteen days of life were only about one-fifth of those of adults on the basis of surface area, and later it was shown that the clearances were lower still in premature babies.[72] This appeared at the time to explain the tendency of babies to become edematous very easily if overtreated with saline, and possibly also to explain their large volumes of extracellular fluid. Since the glomerular filtration rates are about half the adult rates in full-term babies,[70] or a little lower in premature infants,[3] it looks as though the sodium and chloride clearances were so low in early life because tubular reabsorptive activity was overdeveloped relative to glomerular function. The matter, however, is much more complicated for sodium clearances vary so much with the intake of salt[37,38] that this really ought to have been controlled and certainly should be in all future work. Furthermore, the clearance of NaCl in a baby which is getting rid of edema will be very much higher than in a normal baby. Thus Baby G who was edematous excreted 0.085 mEq. Na/hr.[59] till it began to take breast milk and thereafter at an increased rate, whereas Baby H who was not edematous excreted only about 0.028 mEq. Na/hr. Both these babies would have had exceedingly low clearances, for the one with edema would have cleared only about 0.0001 cc./1.73 sq.m./min. and the other one correspondingly less. They represent clearances of starving and dehydrated newborn premature babies but they do show how sodium and chloride clearances can be affected by the excretion of edema fluid. How this in its turn is controlled we do not know.

*Phosphate Clearances.* Plasma phosphates are high in early life but newborn infants may excrete extremely little phosphate. The amounts put out by different babies vary very much, and the same may be true of the amounts excreted by one and the same baby at different times. Dean and McCance[14] found the clearances to range from 0.10 to 3.8 cc./sq.m./min. Adult clearances are of the order of 10 cc./sq.m./min. It is usually accepted[46] that the phosphates in the urine are those which have not been reabsorbed. No one has yet made simultaneous determinations of the phosphate clearances and glomerular filtration rates in infants, but it is evident from what is known about the general level of glomerular filtration rates in infancy that the very low phosphate clearances must be due to exaggerated or unbalanced reabsorption by the tubules.

*Acid-base Regulation.* It is generally agreed[39] that newborn infants very often have an internal acidosis; that is to say, their serum chlorides are higher and their serum bicarbonates lower than the accepted normal values for adults. (Table 1.) Babies have been given a severe internal chloride acidosis by feeding them on "protein milk,"[12] a preparation enriched with caseinogen precipitated by $CaCl_2$. The product

contained 6.2 m.Mol of calcium, 5.7 m.Mol of chloride and 2 m.Mol of sodium per 100 calories. It is not yet clear why infants should be so intolerant of fixed acids, and a good deal more work will have to be done before all the facts can be explained, but some studies have been made in the last few years which have certainly been a help. Gordon and his colleagues,[27] for example, have studied the response of young infants to the ingestion of ammonium chloride. This was something crying out to be done, but unfortunately the investigators stopped short at six babies and made no strictly comparable adult comparisons. Furthermore, the babies they studied were of variable ages. Their ages were 11, 15, 45, 51, 100 and 122 days, respectively, and the first three were not only younger but premature. They gave the babies 4.84 gm. of ammonium chloride /sq.m. of body surface /day for three days, and with this dosage they lowered the plasma bicarbonate 6 to 8 mEq. /L. The babies excreted most of the chloride administered and they all raised their ammonia coefficients and increased their output of ammonia. Two of the three premature babies excreted a much smaller percentage of the additional chloride in combination with ammonia than the larger babies—and a larger percentage in combination with sodium—but the third and youngest premature baby excreted as much of the additional chloride with ammonia as two of the other children. The authors concluded that the ability to form ammonia may be defective in some premature infants and this is certainly possible. Hoffman et al.[33] studied the effects of protein milk on the serum chemistry and urinary response of premature and full-term infants. All showed a fall in plasma bicarbonate, sometimes to a level as low as 10 or 11 mEq. /L., but the study of the urinary response was marred by unavoidable contaminations with saprophytic ammonia-forming organisms. The authors seem to have been so worried by this that they did not trust their results even as much as they might have done. More ammonia was always excreted when the babies were taking protein milk but owing to the raised N intake (due to the protein milk) the ammonia coefficient did not always rise and sometimes fell. A most significant observation, if it can be confirmed, is that the pH of the urine did not as a rule fall to 5 or below and sometimes even rose a little. An examination of the figures as a whole suggests that this was not due to bacterial formation of ammonia, and one of Gordon et al.'s children showed a similar fixity of pH.[27] It is possible that some or all infants may be discovered to be unable to lower, and perhaps also to raise, the pH of their urines to adult limits.[41] Some of the babies excreted much more sodium than others, but the general interpretation of the data is complicated by the fact that the intakes were changed by the protein milk. Robinson[54] who has been studying the production of ammonia by tissue slices *in vitro* has found that the ability of newborn rat kidney cortex to make ammonia in an acid medium at pH 5.8 is very much less than that of adult rat kidney cortex. These papers taken together suggest that the mechanism of ammonia formation may be relatively undeveloped in some infants, but it is clear that the observations already made on infantile acidosis, urinary pH and allied matters are unlikely to be explained by that alone. McCance and von Finck[41] approached the matter in another way. They made a study of normal full-term infants' urines and compared them with those of normal adults. They found on the whole higher ammonia coefficients among the infants and higher ratios of ammonia /titratable acidity. There is no suggestion of defective ammonia formation here[33] but it must be remembered that these were normal babies under no induced stress to produce ammonia. The explanation of these high ammonia excretions and also of the fact that the organic acids accounted for far more of the titratable acidity of the urine of infants than of adults (Fig. 8) was found to lie in the small amount of phosphates in the urine at that age. It is owing to the large

amounts of the buffer phosphates in the urine that adults can excrete so much of their organic acids "free."[46] The paucity of phosphates in infant urines must be a great handicap to them in excreting acids and may explain many of the accepted facts about their susceptibility to an acidosis.

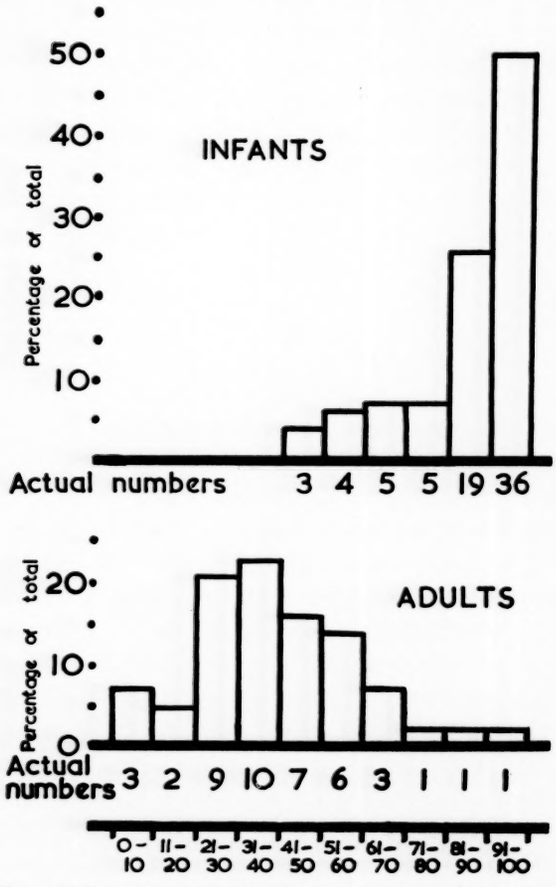



FIG. 8. Frequency distribution diagrams of the percentage of the titratable acidity due to organic acids (horizontal scale) in the urines of infants and adults.[41] (Courtesy of *Arch. Dis. Childh.*, 22: 200, 1947.)

*Osmotic Diuresis during Hydropenia.* Dehydration is a danger which may attend disease at all ages, but it is far more frequent and serious in infancy than it is in adult life. The usual consequences are a rise in the serum urea and sodium salts, and papers have been published in many languages on the serum chemistry of dehydrated infants. Rapoport[50] and Prader and Rossi[47] have recently reviewed the literature and added fresh data. The urine volumes are small. Some years ago it was recognized that dehydration might be induced or enhanced with great rapidity by administering substances which acted as osmotic diuretics to people or animals who were at the same time deprived of water. Hypertonic solutions of urea and sodium chloride were used by the authors Dean and McCance,[15] Elkinton and Winkler.[22] It was at once found out that this produced a diuresis, an observation which had in point of fact been made many years earlier.[19,25] This interesting aspect of renal function and indeed the whole aspect of osmotic diuresis has now been studied by a number of workers[51,52,57,68,69] and many substances other than urea and sodium chloride have been used to produce the effects. Among these may be mentioned mannitol, p-amino hippuric acid, glucose and sorbitol, and it would appear that the extent of the diuresis depends upon the osmotic pressure of the solutes being excreted in the urine and not upon the way in which the substance is excreted by the kidney.[15,52] Although the results obtained by the different investigators do on the whole agree, there are some points on which the results of Seldin and Tarail[57] do not agree with those of Rapoport et al.,[51,52] and there is still little agreement about the interpretation of the results or the exact cause of the fall in the osmotic pressure of the urine. An extensive discussion of the excretion of water and electrolytes under the influence of an osmotic diuresis may be found in the monograph by Kruhøffer.[36] In spite of these difficulties and uncertainties which are inseparable from the early stages of most new methods of approach nothing shows up the resemblances and differences between the renal function of infants and adults so well as a study of the behaviour of the kidney at the two ages under the stress of an osmotic diuresis during hydropenia. Figure 9, which is taken from a paper by Dean and McCance,[15] shows the results which were obtained when urea was used to provoke the diuresis. The changes in the plasma were, as it was intended, similar, but the adult had a rapid diuresis which led to an initial fall in the concentration of urea in the urine

and, incidentally, also in osmotic pressure; whereas the infant had a much smaller but rather more prolonged diuresis, and an initial and continuous rise in the concentration of urea and the osmotic pressure of the urine. When sodium chloride was used

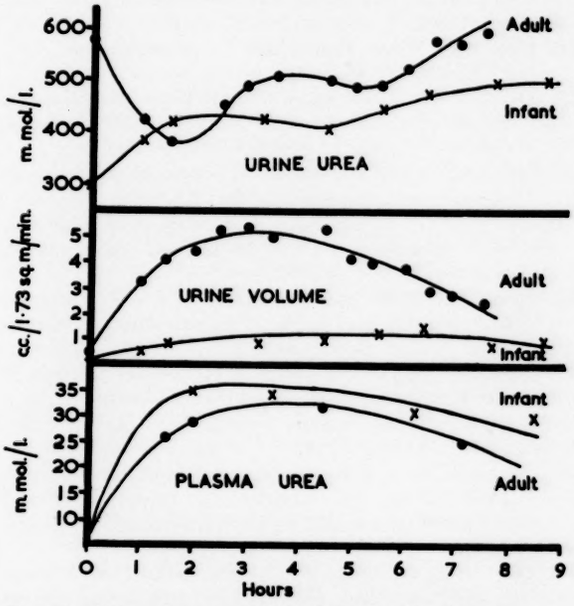



FIG. 9. Urine urea, urine volume and plasma urea following the administration of hypertonic urea to an adult and an infant.[15] (Courtesy of *J. Physiol.*, 109: 81, 1949.)

to raise the osmotic pressure of the body fluids, the adults got an intense diuresis whereas the infants' diureses were again very small and rather more prolonged. In spite of these obvious differences, however, sodium chloride raised the glomerular filtration rate at both ages, and an investigation of the osmotic work carried out by the kidneys showed that the changes due to the diuresis were essentially the same at both ages. (Fig. 10.) The available evidence indeed suggests that the kidneys of adults and newborn infants function in essentially the same way, and that the differences which we observe and which may be of great clinical importance are quantitative rather than fundamental.

## CONCLUSIONS

The last ten years have seen great advances in our knowledge of the function of the kidney in early life. Many of the functions appear to be relatively undeveloped at birth and this may be due to anatomic or haemodynamic reasons or to differences in cellular chemistry. The kidney is not the only organ of excretion to acquire its functional development after birth for the liver

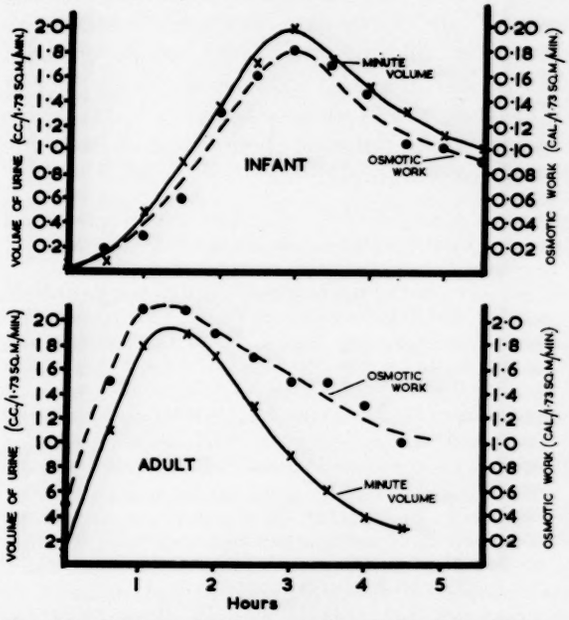



FIG. 10. Changes in the osmotic work of the kidney and in the minute volume of the urine after the administration of hypertonic saline to an infant and an adult. Note that the scale for the infant's osmotic work and urine volume is 1/10 that of the scale for the adult's.[15] (Courtesy of *J. Physiol.*, 109: 81, 1949.)

clearly does so.[23,45] Some of the discoveries about renal function in infancy have had considerable practical importance and details are being filled in every day, but the work so far has been largely descriptive. This is always the first stage but it is disappointing that so far so few of the differences between adults and infants have been explained or have helped to explain observations previously made. In fact, much as our knowledge of kidney function has advanced in the last thirty years, these discoveries about the infant kidney have served only to indicate how little we really do know about the reabsorption of sodium chloride, for instance, or the enzyme mechanisms involved in tubular excretion, or about the osmotic limitations of the cells in the lower nephron. Sooner or later some of the cell physiologists will give us a lead, and

then the differences between infants and adults may very well help us to establish something really fundamental about renal function.

It is almost impossible to write a critical review such as this without misinterpreting some of the data and perhaps hurting the feelings of investigators much more eminent than myself. It is also too easy to fail to refer at all to work which may be of great importance. If I have done either of these things, I hope my colleagues will forgive me.

REFERENCES


1. Adolph, E. F. Physiological Regulations. Lancaster, Pa., 1943. Jaques Cattell Press.
2. Barlow, A. and McCance, R. A. The nitrogen partition in newborn infants' urine. *Arch. Dis. Childhood*, 23: 225, 1948.
3. Barnett, H. L., Hare, K., McNamara, H. and Hare, R. Measurement of glomerular filtration rate in premature infants. *J. Clin. Investigation*, 27: 691, 1948.
4. Barnett, H. L., Hare, W. K., McNamara, H. and Hare, R. S. Influence of post-natal age on kidney function of premature infants. *Proc. Soc. Exper. Biol. & Med.*, 69: 55, 1948.
5. Barnett, H. L., McNamara, H., Hare, R. S. and Hare, K. Inulin, urea, mannitol and PAH clearance ratios in premature infants. *Federation Proc.*, 7: 5, 1948.
6. Barnett, H. L., McNamara, H., Schultz, S. and Thompsett, R. Renal clearances of sodium penicillin G, procaine penicillin G, and inulin in infants and children. *Pediatrics*, 3: 418, 1949.
7. Barta, L. and Hernadi, A. Water-reabsorbing capacity of tubular system in the newborn and in infants. *Am. J. Dis. Child.*, 79: 467, 1950.
8. Baxter, J. S. and Yoffey, J. M. The post-natal development of renal tubules in the rat. *J. Anat.*, 82: 189, 1948.
9. Brod, J. and Sirota, J. H. The renal clearance of endogenous creatinine in man. *J. Clin. Investigation*, 27: 645, 1948.
10. Daly, H., Wells, L. J. and Evans, G. Experimental evidence of the secretion of urine by the fetal kidney. *Proc. Soc. Exper. Biol. & Med.*, 64: 78, 1947.
11. Dansis, J., Birmingham, J. R. and Leslie, S. H. Congenital diabetes insipidus resistant to treatment with pitressin. *Am. J. Dis. Child.*, 75: 316, 1948.
12. Darrow, D. C., Da Silva, M. M. and Stevenson, S. S. Production of acidosis in premature infants by protein milk. *J. Pediat.*, 27: 43, 1945.
13. Dean, R. F. A. and McCance, R. A. Inulin, diodone, creatinine and urea clearances in newborn infants. *J. Physiol.*, 106: 431, 1947.
14. Dean, R. F. A. and McCance, R. A. Phosphate clearances in infants and adults. *J. Physiol.*, 107: 182, 1948.
15. Dean, R. F. A. and McCance, R. A. The renal responses of infants and adults to the administration of hypertonic solutions of sodium chloride and urea. *J. Physiol.*, 109: 81, 1949.
16. Desmond, M. M. and Sweet, L. K. Relation of plasma proteins to birth weight, multiple births and edema in the newborn. *Pediatrics*, 4: 484, 1949.
17. Dicker, S. E. Effect of the protein content of the diet on the glomerular filtration rate of young and adult rats. *J. Physiol.*, 108: 197, 1949.
18. Doxiadis, S. A. Azotaemia in infancy. *Arch. Dis. Childhood*, 23: 50, 1948.
19. Dreser, H. Über Diurese und ihre Beeinflussung durch pharmakologische Mittel. *Arch. f. exper. Path. u. Pharmakol.*, 29: 303, 1892.
20. Dupont, A. Investigations on serum bicarbonate in prematures. *Acta pædiat.*, 77: 113, 1949.
21. Effersøe, P. Comparative tests of the creatinine and thiosulphate clearance in kittens. *Acta physiol. Scandinav.*, 20: 91, 1950.
22. Elkinton, J. R. and Winkler, A. W. Transfers of intracellular potassium in experimental dehydration. *J. Clin. Investigation*, 23: 93, 1944.
23. Fashena, G. J. Mechanism of hyperbilirubinemia in the newborn infant: experimental demonstration of functional hepatic immaturity. *Am. J. Dis. Child.*, 76: 196, 1948.
24. Fellers, F. X., Barnett, H. L., Hare, K. and McNamara, H. Change in thiocyanate and sodium$^{24}$ spaces during growth. *Pediatrics*, 3: 622, 1949.
25. Galeotti, G. Über die Arbeit, welche die Nieren leisten, um den osmotischen Druck des Blutes auszugleichen. *Arch. Anat. u. Physiol.*, p. 200, 1902.
26. Gordon, A. H. An investigation of the intracellular fluid of calf embryo muscle. *Biochem. J.*, 45: 99, 1949.
27. Gordon, H. H., McNamara, H. and Benjamin, H. R. The response of young infants to ingestion of ammonium chloride. *Pediatrics*, 2: 290, 1948.
28. Heller, H. The renal function of newborn infants. *J. Physiol.*, 102: 429, 1944.
29. Heller, H. Antidiuretic hormone in pituitary glands of newborn rats. *J. Physiol.*, 106: 28, 1947
30. Heller, H. The response of newborn rats to the administration of water by the stomach. *J. Physiol.*, 106: 245, 1947.
31. Heller, H. Effects of dehydration on adult and newborn rats. *J. Physiol.*, 108: 303, 1949.
32. Heller, H. and Zaimis, E. J. The antidiuretic and oxytocic hormones in the posterior pituitary glands of newborn infants and adults. *J. Physiol.*, 109: 162, 1949.
33. Hoffman, W. S., Parmelee, H. H. and Grossman, A. Mechanism of production of acidosis in premature infants by protein milk. *Am. J. Dis. Child.*, 75: 637, 1948.
34. Kerpel-Fronius, E. Über die Wechselbeziehungen zwischen Kochsalz und Reststickstoff. *Ztschr. f. d. ges. exper. Med.*, 85: 235, 1932.
35. Kerpel-Fronius, E. Die Nierenfunktion bei der Exsiccose. *Ztschr. f. Kinderh.*, 51: 400, 1932.
36. Kruhøffer, P. Studies on Water-electrolyte Excretion and Glomerular Activity in the Mammalian Kidney. Rosenkilde and Bagger, Copenhagen. London. 1950. H. K. Lewis & Co. Ltd.

37. Ladd, M. and Raisz, L. G. Response of the normal dog to dietary sodium chloride. *Am. J. Physiol.*, 159: 149, 1949.
38. Leaf, A., Couter, W. T. and Newburgh, L. H. Some effects of variation in sodium intake and of different sodium salts in normal subjects. *J. Clin. Investigation*, 28: 1082, 1949.
39. McCance, R. A. Renal function in early life. *Physiol. Rev.*, 28: 331, 1948.
40. McCance, R. A. Studies of undernutrition. Wuppertal 1946–1949. Aspects of renal function and water metabolism. Spec. Rep. Ser. Med. Res. Council, Lond., No. 275, 1950, (in the press).
41. McCance, R. A. and von Finck, M. A. The titratable acidity, pH, ammonia and phosphates in the urines of very young infants. *Arch. Dis. Childhood*, 22: 200, 1947.
42. McCance, R. A. and Widdowson, E. M. Blood-urea in the first nine days of life. *Lancet*, 1: 787, 1947.
43. McCance, R. A. and Wilkinson, E. The response of adult and suckling rats to the administration of water and of hypertonic solutions of urea and salt. *J. Physiol.*, 106: 256, 1947.
44. McCance, R. A. and Young, W. F. The secretion of urine by newborn infants. *J. Physiol.*, 99: 265, 1941.
45. Mollison, P. L. and Cutbush, M. Bromsulphalein excretion in the newborn. *Arch. Dis. Childhood*, 24: 7, 1949.
46. Pitts, R. F. and Alexander, R. S. Renal reabsorptive mechanism for inorganic phosphate in normal and acidotic dogs. *Am. J. Physiol.*, 142: 648, 1944.
47. Prader, von A. and Rossi, E. Hyperelektrolytämie (Hypertonie und Hyperosmie der Körpersäfte) bei Wassermangel, Elektrolytüberdosierung, renalen und endokrinen Störungen. *Helvet. paediat. acta*, 4: 482, 1949.
48. Pratt, E. L., Bienvenu, B. and Whyte, M. M. Concentration of urine solutes by young infants. *Pediatrics*, 1: 181, 1948.
49. Raaschou, F. Dissociation between glomerular and tubular renal function in cases of pyelonephritis. *Acta med. Scandinav.*, 114: 414, 1943.
50. Rapoport, S. Hyperosmolarity and hyperelectrolytemia in pathologic conditions of childhood. *Am. J. Dis. Child.*, 74: 682, 1947.
51. Rapoport, S., Brodsky, W. A., West, C. D. and Mackler, B. Urinary flow and excretion of solutes during osmotic diuresis in hydropenic man. *Am. J. Physiol.*, 156: 433, 1949.
52. Rapoport, S., West, C. D. and Brodsky, W. A. Excretion of solutes and osmotic work during osmotic diuresis of hydropenic man. The ideal and the proximal and distal tubular work; the biological maximum of work. *Am. J. Physiol.*, 157: 363, 1949.
53. Robinson, J. R. Osmoregulation in surviving slices from the kidneys of adult rats. *Proc. Roy. Soc. B.*, (in press).
54. Robinson, J. R. Personal communication.
55. Rotke-Meyer, A. Serum protein and blood urea in prematures on high protein nutrition. *Acta pædiat.*, 38: 551, 1949.
56. Rubin, M. I., Bruck, E. and Rapoport, M. Maturation of renal function in childhood: clearance studies. *J. Clin. Investigation.*, 28: 1144, 1949.
57. Seldin, D. W. and Tarail, R. Effect of hypertonic solutions on metabolism and excretion of electrolytes. *Am. J. Physiol.*, 159: 160, 1949.
58. Shannon, J. A. Glomerular filtration and urea excretion in relation to urine flow in the dog. *Am. J. Physiol.*, 117: 206, 1936.
59. Smith, C. A., Yudkin, S., Young, W., Minkowski, A. and Cushman, M. Adjustment of electrolytes and water following premature birth. *Pediatrics*, 3: 34, 1949.
60. Suranyi, J. and Zimanyi, S. Endogenous creatinine clearance in infancy and early childhood. *Lancet*, 1: 653, 1948.
61. Svendsen, A. Investigations on potassium in infants. *Acta pædiat.*, 77: 146, 1949.
62. Tayler, E. The regulation of the internal environment in newborn and very young animals. Thesis, London University, 1949.
63. Thomson, J. Observations on the urine of the newborn infant. *Arch. Dis. Childhood*, 19: 169, 1944.
64. Thomson, J. Urea clearance in the immediate postnatal period. *Arch. Dis. Childhood*, 24: 180, 1949.
65. Vegter, A. W. Papier-chromatographie en haar toepassing in de klinik. *Maandschr. v. kindergeneesk.*, 17: 146, 1949.
66. Vesterdal, J. A simple method of estimating the inulin and para-amino-hippurate clearances in newborn infants. *Acta pædiat.*, 37: 421, 1949.
67. Vesterdal, J. and Tudvad, F. Studies on the kidney function in premature and full-term infants by estimation of the inulin and para-amino-hippurate clearances. *Acta pædiat.*, 37: 429, 1949.
68. Wesson, L. G., Jr. and Anslow, W. P., Jr. Excretion of sodium and water during osmotic diuresis in the dog. *Am. J. Physiol.*, 153: 465, 1948.
69. Wesson, L. G., Jr., Anslow, W. P., Jr. and Smith H. W. The excretion of strong electrolytes. *Bull. New York Acad. Med.*, 24: 586, 1948.
70. West, J. R., Smith, H. W. and Chasis, H. Glomerular filtration rate, effective renal blood flow, and maximal tubular excretory capacity in infancy. *J. Pediat.*, 32: 10, 1948.
71. Williamson, R. C. and Hiatt, E. P. Development of renal function in fetal and neo-natal rabbits using phenolsulphonphthalein. *Proc. Soc. Exper. Biol. & Med.*, 66: 554, 1947.
72. Young, W. F., Hallum, J. L. and McCance, R. A. The secretion of urine by premature infants. *Arch. Dis. Childhood*, 16: 243, 1941.
73. Young, W. F. and McCance, R. A. The secretion of urine by dehydrated and normal infants. *Arch. Dis. Childhood*, 17: 65, 1942.

# Clinic on Psychosomatic Problems

## A Child's Reaction to Adenoidectomy

THESE cases are chosen to illustrate the relation between psychiatric and medical factors in the production of symptoms. They are part of the Harvard teaching on the Psychiatric and Children's Medical Services of the Massachusetts General Hospital. These psychiatric conferences are edited by Drs. Stanley Cobb and Henry H. W. Miles. Publication is made possible by a grant from the Josiah Macy, Jr., Foundation.

DR. SAMUEL KAPLAN: For more than a year we have been studying the responses of an unselected group of children to tonsillectomy and adenoidectomy. This has been primarily observation, with no therapeutic intention, and has been accomplished by interviewing the patient and mother at the time of hospitalization and then at intervals later for follow-up. We are presenting the case of Richard N. (No. 407070) a ten year old boy who had a dramatic reaction following operation.

MISS BESSIE FAIR: The mother was pregnant eight months at the time of Richard's operation but was quite willing to cooperate with us. She said that her health was good except for itching if she wore wool clothing, and described herself as being placid in all situations. Her husband, six years her senior, was "very nervous" and had a "stomach ulcer." She said that he was a man who always kept "everything held in," worried a lot and took his responsibilities very seriously.

Richard is the second of three siblings, having an older brother who is "tougher" and who enjoys rough sports such as football. The younger sister does not present any problems except for recurrent "eczema."

The patient was a full-term baby although he weighed only 5 pounds, 3 ounces at birth. Delivery was said to have been normal. The mother was unable to nurse him but there were no feeding problems. He was weaned from the bottle at eleven months. Richard learned to walk before he was a year old but did not speak plainly until he was two and a half years old. Bladder and bowel control were achieved easily at about a year. The patient never had any phobias, night terrors or temper tantrums. He sucked his thumb for several years but finally gave up the habit. Richard started school when he was five and a half and has always had some difficulty. He is repeating the fourth grade this year. The school problem had been attributed to his subnormal hearing and he has been given instruction in lip reading.

The mother says Richard is "babyish" for his age and reports that his teachers have said the same thing. He is not fond of active, rough games but rather prefers playing quietly with children younger than himself. The mother attributes this to the fact that, because of many illnesses, he has received more protection and attention than the other children.

The patient's medical problems began at an early age. There was infantile eczema about which we have no detailed information. Bilateral otitis media developed when he was nine months old and recurred many times during the ensuing four years. When he was five, he had an acute mastoiditis treated conservatively after which a tonsillectomy was done. He spent three weeks in a hospital at that time and was not apparently disturbed by the experience. Other childhood illnesses included measles, mumps and chicken pox. After the latter subsided, there was an episode of atopic dermatitis which lasted for several months, evidently the same type of skin trouble that his sister has.

The patient was referred to the Massachusetts Eye and Ear Infirmary because of hearing loss, and an adenoidectomy was advised. When brought to the hospital for the operation he admitted to his mother

that he was afraid. His mother tried to reassure him by saying that they were not going to take his tonsils out, but only his adenoids. She admitted to the doctor her own confusion in preparing Richard for the operation by saying she did not know whether he was sure he would be operated upon or not. Maybe he thought only that his throat would be sprayed. The doctor also discussed with her the problem of Richard's undescended testicle. Richard has been worried lest he would be hospitalized again and operated upon for that.

DR. KAPLAN: Preoperative physical examination revealed that both ear drums were thickened and dull. There were tonsillar remnants present and x-ray evidence of enlarged adenoids. There was a hearing loss of the conduction type; in the whispered voice test, hearing was 12/20 A.D. and 1/20 A.S. Hearing loss by audiometer test was approximately 20 per cent on the right and 35 per cent on the left. The left testicle was not palpable either in the scrotum or the inguinal canal. Routine blood and urine examinations were normal.

I first saw the patient on the day of admission to the hospital (the day preceding operation). He was a sturdy, good-looking boy who did not appear upset as he told me that his adenoids needed to be taken out. He said that his tonsils had been taken out when he was five but some grew back. Richard admitted readily that he was scared about the operation. He did not know how the adenoids would be removed, and his mother had told him he would be given ether which he did not like.

Richard talked freely about school and his play activities with other boys. He told many stories interwoven with the motif of mutilation. One such was the mishap which had befallen his dog. The latter had snapped up a baited fish-hook and had to have the hook removed by a neighbor. The dog was not given any ether and his mouth had been torn badly. The patient also graphically described a man who sells pencils, who has one leg missing. Another man who lives nearby is blind. He talked of a boy he knows who "hops rides" on cars despite his parents' warnings. This boy fell and "broke his arm in three places on the same day."

The patient told me that his mother was going to have a new baby. He has tried to find out where the baby comes from and she has told him that the nurse at the hospital will give it to her. Richard was clearly dubious of this explanation but accepted it because his mother had given it to him.

Finally, he admitted that what worried him most about the operation was the ether. Last time, after having ether, he vomited a lot and he is afraid it will happen again.

During the second day in the hospital, while awaiting the operation, the patient was quite concerned with the topic of death. He said that his dog had died as a result of a kick in the chest. An x-ray had been taken but the dog died anyway. (During the morning Richard had had a routine chest x-ray.) He reported that he had been unable to sleep the night before and although he denied being scared, he was fidgety and tense. He talked of a dog that chased cars and had been run over several times but never killed. He said that his friends "hopped rides" on cars but he did not. His mother had told him that if he did, he might get killed and he did not want to take the chance.

Adenoidectomy was performed and the tonsillar tags were removed as well. Surgically speaking the operation and the convalescence were uneventful.

Psychologically, Richard's postoperative reaction was dramatic. For four days he could not talk at all, indicating by gestures in response to direct questions that he was in great pain, that he had vomited a lot just as he had feared and that he was worried whether his voice would ever come back. He then began talking in a high squeaky tone. He ate very poorly, drooled and expressed concern because he did not know what the doctors had done to him. For about two weeks he showed a tendency to invalidism, then gradually relinquished his

symptoms. His voice returned to normal, his appetite improved and he went back to school. He said that the second operation had been necessary to help his hearing and claimed that his hearing was better. However, he said, "My brother had *his* tonsils taken out only *once* and I don't understand that. Maybe some people have only one operation." He said that his aunt went to the hospital to have her appendix out and when asked where the appendix was he pointed to the upper thigh. He does not know why anybody should have to have their appendix out.

Miss Fair: About a month after operation Richard's eczema flared up again. His mother had gone to the hospital in false labor and his grandmother brought him to us for a follow-up visit. I have learned since that the mother was disappointed because Richard's operation did not improve his hearing and also that she was angry and upset because we only talked to him and did not prescribe treatment for the dermatitis.

DISCUSSION

Dr. Kaplan: He produced some interesting material. On the first day in the hospital the fantasies expressed his overwhelming fear of mutilation, namely, mention of the dog's mouth being torn, the man who limped, the blind man and the final story of the boy who disobeyed and broke his arm in three places. His great concern about the impending operation was probably intensified by his experiences during the routine preoperative physical examination. He then learned that he had a "missing" testicle and that the doctors might "operate on him" for this.

On the second day just before the operation when his anxiety was at its height, there were the stories of death. His dog was kicked in the chest, another dog was run over because he chased cars and did forbidden acts.

The evidence points to his identification with the dog, associating his operation with the dog's torn mouth. Also, dogs chase cars and he is forbidden to hop rides on cars. The disobedient boy was hurt because he did not obey. He also had made some remarks about his own and his sister's itching and that she has to wear mittens so that she will not scratch, but he does not need mittens. He is a good boy. (He does not indulge in forbidden acts.) What the fear of vomiting means, I do not know.

Dr. Lucie Jessner: Did his mother vomit during this pregnancy?

Dr. Kaplan: I do not know. I have not been able to find out. His behavior after operation was unusual, with the drooling and the squeaky voice. The aphonia for four days, together with the fears about operation, led us to believe that he had expected that some mutilating operation would be done. It would be interesting to know more, to have him return for psychotherapy. He is a neurotic boy and the operation accentuated his anxiety. He has not worked it through but has just given up some symptoms.

Dr. Stanley Cobb: Some of his worry about hospitals and where babies come from might be expected, but he had this in an exaggerated form. This is partly because of his former experience with operation, ether and vomiting (that is related to reality) and partly because of the coincidence of this operation with his mother's pregnancy. Do you think he is ignorant about childbirth?

Dr. Kaplan: I do not think so. He would not explain his fantasies but in the section of the city in which he lives the children know a lot about sexual behavior and reproduction. His brother knew. The facts that his mother was almost at term and that he was in the hospital for an operation stimulated the production of fantasies.

Dr. Cobb: Do you think it is lack of knowledge or lack of courage to face it? That is important in clarifying his anxiety and neurosis. How does it fit in with his psychologic picture? The rest is fear of mutilation.

Dr. Kaplan: We should know more about the boy. Now he says he wants to be a bachelor and a hermit, believing that he does not have the qualifications for another kind of life.

Dr. Cobb: I also wondered about his intelligence. He did not talk until he was two and a half and repeated a grade later on. Do you think he is on the stupid side?

Dr. Kaplan: I do not know. I.Q. tests have not been done. He did not impress me as stupid.

Dr. Gertrud C. Reyersbach: He ought to be re-examined. If the testicle is still undescended we should make up our minds whether to do anything about it.

Dr. Cobb: Is this because of fear of malignancy?

Dr. Reyersbach: Testicles which are undescended at puberty usually atrophy. There is also a greater tendency to malignancy than in descended testes. Therefore, he should be operated upon now if he has an undescended testis.

Dr. Cobb: Won't that scare him? He already has fears of operations and of being mutilated if operated upon. We ought to weigh his anxiety against your fear of malignancy.

Dr. Reyersbach: We would reassure him. It is possible to explain to a ten year old that he is adequate and that the operation does not matter. We can reassure him about being a "complete person." Boys we have followed have not been frightened, mostly because of the reassurance.

Dr. Cobb: The main thing is a skillful approach. It could be handled very badly.

Dr. Jessner: I would think the method of preparation would make a great difference. This boy was sure his mother did not tell him everything. She told him that the nurses would give her the baby at the hospital and he did not believe that that was the whole story. Then when he was told that he was to have an adenoid operation, he thought that more would be done, too. I think that if this could be worked through with him, it would help. Now he has fears of what is still to be done. He resigns himself to being a hermit.

He knows more than he wants to express. His mother tells us that he does not speak out and that he is a good boy. He suppresses his knowledge as if to prove his innocence and "goodness."

Dr. Reyersbach: We should be truthful in our explanations and be sure that he understands. We should not do what I observed in Germany in 1934 and 1935 when many boys were coming to the hospitals to be circumcised. At least 50 per cent of them had been told they were having their tonsils out. There was an awful lot of puzzlement after the circumcision and we had a terrible time reassuring them. Parents have tended to use the tonsils as a scapegoat for everything. If the children have colds, it is their tonsils. If they wet the bed, it is their tonsils. Even if they are tired, it is because of their tonsils.

Dr. Kaplan: They expect all sorts of conditions to be better after the tonsils are removed.

Dr. Jessner: The parents of one feeble-minded girl even wanted her to have a tonsillectomy so she would be brighter.

Dr. Thomas Dwyer: I have a comment to make about the way the project itself has been managed. This mother shows us that something needs to be done about follow-up methods. If the boy's dermatitis had been treated, the mother would not have gotten angry. I wonder how many other mothers get angry because they see only a psychiatrist and no one seems interested in the other problems.

Dr. Reyersbach: Unfortunately, we do not always treat the family and the patient in the clinic as if we went to the home as the family doctor. This boy should have gotten the proper examination to be certain whether there is or is not an undescended testicle. The condition should have been explained to the mother and to the boy in the proper way, taking them into our confidence. He would not need a surgical consultation. The same applies to the skin problem; the Children's Medical Clinic should have kept tabs on this instead of sending him all around. I should think that one clinic with good management could have handled the patient by a single doctor.

Dr. Dwyer: The family has no relationship to the hospital as a whole.

Dr. Cobb: That is the price of modern medicine.

DR. REYERSBACH: Yes, and this is not criticism but a statement of failure of the procedure.

COMMENT

This case illustrating the repercussions of a "minor" operation upon a ten year old boy was selected not only to show his overt symptoms but also to indicate, at least partially, their meaning and to sketch briefly some important psychodynamic aspects of the mother-child relationship and the family-hospital relationship.

The patient was one of an unselected group of children whose emotional reactions to tonsillectomy and adenoidectomy were studied psychiatrically.[1] At the time of his operation he was in the midst of a neurotic conflict, the major components of which were brought out in the presentation.

In retrospect, from the vantage point of the psychiatric observer, the case shows us several things that should have been managed differently. The problem of the undescended testicle could have been dealt with in a manner less frightening to the boy. Richard's curiosity about his mother's pregnancy and his anxiety about what the doctors would do to him needed a truthful explanation, instead of the confusing misinformation which his mother gave him. Very frequently one sees this sort of problem, namely, a mother who knows intellectually just how to deal with a child (often from extensive readings in child psychology) but who, nevertheless, due to unconscious motivations cannot carry out the logical procedure but in one way or another perpetuates her own neurotic patterns.

Some of the material (omitted from the case presentation for brevity) revealed that the mother had always been greatly concerned about Richard's ears. When he had had mastoiditis at the age of five she had expected that an operation would "make his ears better." She had been disappointed. Then came the adenoidectomy, performed in the hope that his hearing would be improved; again she was disappointed and needed only an incidental excuse to become angry at the hospital. The fact that no treatment was offered for Richard's dermatitis gave her a rationalization which covered the "deeper" aspects of her resistance. The interpretation might also be advanced that because of her overprotection (the unconscious wish that her son remain a baby) she was reluctant to bring the boy back for a decision about the testicle. As was suggested in the discussion, had the mother been handled more skillfully in the clinic by a physician who could establish a secure doctor-patient relationship it would have been easier to dissipate her conscious resentments and fears, thereby paving the way for a working through of the less conscious conflicts.

Jessner and Kaplan[1] in a preliminary report of their study have found that all children in the group experienced some degree of anxiety in connection with the operation but most of them were able to tolerate the experience without any lasting emotional sequelae. Those who did have disturbing reactions were for the most part children who already had neurotic problems. Some general suggestions were discussed in the report which could be applied to elective surgical procedures in general. These dealt with the most favorable age range in which to operate upon children, the postponement of operations if there had been recent traumatic experiences, the emotional preparation of the child by parents and physician, the recognition of the symbolic value to the child of arbitrary or trivial requests and the maintenance of good ward morale.

It is hoped that a more thorough understanding and acceptance by parents, physicians, hospital administrators and ward personnel of the psychologic implications of surgical procedures upon children will lead to hospital routines which are flexible enough to meet the needs of the individual child.

[1] JESSNER, L. and KAPLAN, S. Observations on the emotional reactions of children to tonsillectomy and adenoidectomy—a preliminary report. *Tr. Conf. Prob. Infancy & Childhood*, 3: 97, 1949.

# Clinico-pathologic Conference

## Renal Insufficiency*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, Jr., M.D., of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, B. B. (No. 155678), was a white single male grocery clerk, twenty-three years of age, who entered the Barnes Hospital for the first of seven admissions on February 9, 1948, because of swelling of the legs and headache. The family history was non-contributory but the past history was of interest in that at the age of six the patient had a tonsillectomy. When he was twelve he had acute inflammation of several joints and was in bed for about four months; a physician who saw him at that time made a diagnosis of rheumatic fever. When he was twenty-one he had an upper respiratory infection which subsided after three days of treatment with a sulfonamide drug. He denied having had scarlet fever.

The patient said that following the episode of rheumatic fever his urine had the color of rust for a short period of time. Subsequently, he had persistent nocturia. When he was nineteen he was rejected by the Army because of albuminuria; at that time he was symptom-free. One year later, however, he first noted swelling of the lower extremities and soon thereafter developed a rather severe backache. He was treated in another hospital where he was advised to follow a low salt, low protein diet. He adhered to this regimen and his backache disappeared but the ankle swelling persisted. Two months prior to his first admission to the Barnes Hospital he developed severe headaches which came on in the morning; occasionally they were associated with vomiting. He also was troubled during this period by frequent nosebleeds. He consulted a physician who told him his blood pressure was high and advised his entry into the Barnes Hospital.

Physical examination at the time of entry revealed the temperature to be 37.4°C., pulse 104, respirations 24 and blood pressure 210/140. The patient appeared pale and chronically ill. The arterioles in both fundi were narrowed and a small linear hemorrhage was present in the left fundus. Examination of the upper respiratory tract was negative. The lungs were clear to percussion and auscultation. The heart was enlarged 11 cm. to the left of the mid-sternal line in the fifth interspace and the apical impulse was diffuse. There was a short, rough, grade II systolic murmur at the apex which was not transmitted. The aortic second sound was ringing. Abdominal examination was negative. The kidneys could not be palpated. The prostate was normal and there was no peripheral edema.

The laboratory findings were as follows: Blood count: red cells, 2,620,000; hemoglobin, 9.5 gm.; white cells, 8,400; differential count: normal. Urinalysis: specific gravity, 1.012; albumin, 1+; sugar, 2+; centrifuged sediment, negative. Stool examination: guaiac negative. Blood Kahn test: negative. Blood chemistry: non-protein nitrogen, 30 mg. per cent; fasting blood sugar, 98 mg. per cent; total protein, 5.9 gm. per cent; albumin, 3.8 gm. per cent; globulin, 2.1 gm. per cent. Intravenous PSP test: 10 per cent excretion in two hours. Roentgenogram of the chest: Old pleurisy at the left base. Electrocardiogram: diaphasic T waves in lead I.

* From the Departments of Internal Medicine and Pathology, Washington University School of Medicine and the Barnes Hospital, St. Louis, Mo.

The patient was given a regular diet and was quite comfortable at rest. On only one occasion did he complain of headache and at no time did edema appear. Many urinalyses revealed consistent albuminuria, ranging from 2 to 3 plus; the centrifuged sediments showed an occasional hyaline cast and an occasional red cell. The blood calcium was 8.2 mg. per cent and the phosphorus 7.8 mg. per cent. The blood chlorides, $CO_2$ combining power, vital capacity, circulation time, venous pressure, glucose tolerance test and sedimentation rate were within normal limits. The systolic pressure was maintained between 180 and 200 with a diastolic pressure between 130 and 140 mm. of mercury. He was given two units of red cell residue during his hospital stay and his red blood cell count rose to 3,670,000 with 12 gm. of hemoglobin. He was discharged from the hospital on February 20, 1948, and was followed in the hypertension clinic. He was advised to take a low salt diet with 70 gm. of protein.

Following discharge the patient felt quite well; although he had occasional swelling of the ankles and eyelids he was able to work as a clerk in a grocery store. He was admitted for the second time on March 31, 1948, at the request of the staff, for special studies.

Physical examination revealed the temperature to be 36.9°C., pulse 80, respirations 17 and blood pressure 210/135. Examination on this admission revealed slight exophthalmos, more pronounced on the left than on the right. Exudates and hemorrhages were noted in both fundi; otherwise the physical examination was unchanged. Laboratory findings included a red blood count of 3,020,000 with 9 gm. of hemoglobin. Urinalysis revealed a specific gravity of 1.011, 1+ albuminuria and a few red cells in the centrifuged sediment. The non-protein nitrogen was 58 mg. per cent, calcium 8.4 mg. per cent; phosphorus, 8 mg. per cent; and cholesterol, 385 mg. per cent.

The patient was maintained on a 1 gm. salt diet. Transfusions with hypertensive blood induced a moderate rise of blood pressure in the patient whereas there was no significant change in his blood pressure following transfusion with blood from normotensive subjects. There was very little change in mannitol and para-aminohippurate clearances before and after either type of transfusion. The patient was discharged on April 15, 1948, his condition having remained unchanged.

During the nine months between the second and third admissions the patient was troubled by headache, continuous nausea and some edema of the eyes and feet. He was followed regularly in the Hypertension Clinic. During this period he worked some ten to twelve hours a day as a salesman and was on his feet most of this day. He re-entered for further study on January 6, 1949.

At the time of entry physical examination was essentially as before although on this admission neither hemorrhages nor exudates were seen in the eyegrounds. The abnormal laboratory findings were as follows: red cells, 3,100,000; hemoglobin, 7 gm. per cent. Urinalysis: specific gravity, 1.010; albumin, 4+; centrifuged sediment, occasional waxy, granular and hyaline casts and a few red cells per high power field; non-protein nitrogen, 109 mg. per cent; calcium, 7.9 mg. per cent; phosphorus, 10.8 mg. per cent; chlorides, 114 mEq./L.; total proteins, 5.0 gm. per cent.

The patient was maintained on a diet containing 0.5 gm. of salt, a low phosphorus content and 35 gm. of protein. He was given amphojel with each meal. Following two blood transfusions he was symptomatically much improved but at the time of discharge the non-protein nitrogen and blood pressure were as before. The patient left the hospital on April 5, 1949.

Following discharge the patient was followed in the Hypertension and Hematology Clinics and continued to have much the same pattern of symptomatology. He was admitted for further study on June 1, 1949.

Physical examination revealed the blood

pressure to be 230/140. The physical findings were as before. The abnormal laboratory findings included a red blood cell count of 2,400,000; the hemoglobin was 7 gm. Urinalysis showed a specific gravity of 1.006, 4+ albumin and the sediment contained hyaline and granular casts and a moderate number of red blood cells. The non-protein nitrogen was 83 mg. per cent. Soon after admission a phlebotomy was performed; 950 cc. of blood were removed and replaced with 2 units of Rh negative "O" "N" blood from which part of the plasma had been removed. The patient received a total volume of 650 cc. This transfusion was given in order that the survival time of the transfused cells might be followed. Following the transfusion the non-protein nitrogen rose to 140 mg. per cent and fell again to 90 mg. per cent. He was discharged on June 11, 1949, and advised to take a diet low in salt, protein and phosphorus.

During the interval between the fourth and fifth admissions the patient felt somewhat better in that his headaches and nausea were somewhat decreased, but he continued to have some dyspnea. On September 11, 1949, he was re-admitted.

Physical examination revealed the blood pressure to be 212/128. The fundi showed a number of scars but no fresh hemorrhages or exudates. The heart was slightly larger than on previous admission. There was no edema. The laboratory findings were essentially as noted previously.

During his hospital stay the patient received an exchange transfusion; 9,500 cc. of blood were removed, 1,000 cc. at a time, and 4,500 cc. of "O" Rh negative blood and 5,500 cc. of plasma were infused over an eight and one-half-hour period. The patient tolerated the procedure well and at its completion his urine was clear and his serum was free of hemoglobin. There was no change in the circulation time or venous pressure. The non-protein nitrogen fell to 74 mg. per cent. At the time of discharge on September 16, 1949, the non-protein nitrogen was 90 mg. per cent and the blood pressure 190/110.

The patient continued to have headaches, nausea and dyspnea; all of these symptoms increased. On the day before his sixth admission he had a generalized convulsion and was unconscious for several minutes. On November 29, 1949, he entered the hospital again.

Physical examination revealed the temperature to be 37.2°C., pulse 96, respirations 20 and blood pressure 210/140. Examination of the eyegrounds showed slight blurring of the discs and several flame-shaped fresh hemorrhages in the right fundus. The heart was enlarged to the left anterior axillary line but there was no edema. Otherwise the physical examination remained unchanged. Laboratory data were as follows: red blood cell count, 3,117,000; hemoglobin, 9 gm. Urinalysis: specific gravity, 1.010; albumin 3+; centrifuged sediment, granular casts and red cells; non-protein nitrogen, 113 mg. per cent; calcium, 7.1 mg. per cent; phosphorus, 13.5 mg. per cent.

During his hospital stay the patient had two severe episodes of epistaxis. His nausea and headaches improved, however, and at the time of discharge on December 17, 1949, the non-protein nitrogen was 95 mg. per cent.

In the month which elapsed between the sixth and seventh hospital admissions the patient received two blood transfusions weekly as an outpatient. Exertional dyspnea increased markedly and three weeks previous to entry he developed a cough productive of small amounts of sputum which frequently contained bright blood. Otherwise he felt relatively well, however, until five days before admission, when, on the way home from the clinic, he developed a chill followed by fever, headache and nausea. Soon thereafter, ankle and facial edema, nausea and vomiting reappeared. He took a proprietary alkali and baking soda and his edema became worse. He was admitted for the last time on January 14, 1950.

Physical examination revealed the temperature to be 37°C., pulse 100, respirations 24 and blood pressure 210/150. The patient

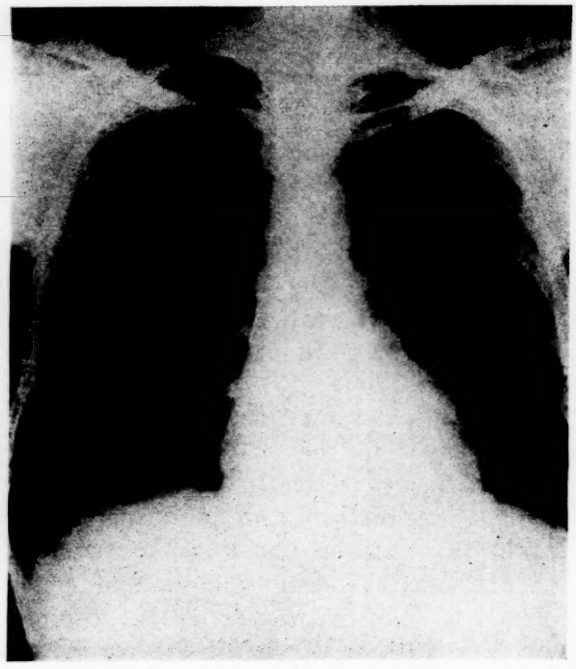


FIG. 1. Chest film taken in December, 1949; the heart is enlarged but the lung fields are clear.

look chronically ill. The skin was markedly sallow and there were a few old petechiae and small ecchymoses over the surface of the body. His face was puffy. Vision was markedly impaired; the fundi showed bilateral blurring of the discs, many fresh hemorrhages and some exudates. Examination of the heart revealed it to be about the same size as on the previous admission but a loud systolic murmur was heard along the left sternal border. Two plus edema of the lower extremities was present.

The laboratory findings were as follows: The blood count and urinalysis were as before. Non-protein nitrogen, 120 mg. per cent; $CO_2$ combining power, 39.5 vols. %; chlorides, 122 mEq./L.; calcium, 7.4 mg. per cent; phosphorus, 7.6 mg. per cent; total protein, 4.6 gm. per cent; albumin/globulin ratio, normal; venous pressure 170 mm. of water. Roentgenogram of the chest revealed enlargement of the cardiac silhouette with parenchymal infiltration in the right lung involving all lobes. Electrocardiogram showed depressed S-T segments and inverted T waves in leads I, II, $V_5$ and $V_6$.

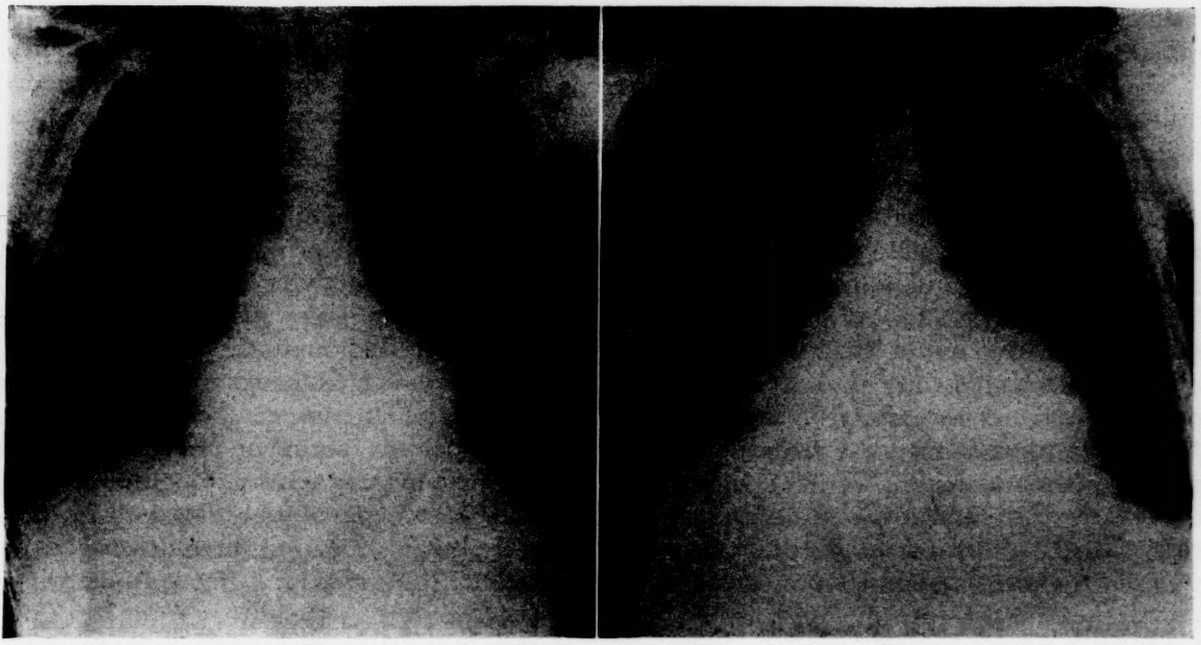
The patient's course was slowly but steadily downhill. He had repeated epistaxes and several convulsions. Further roentgenograms of the chest revealed extension of the pneumonic process in the right lung; despite the pulmonary infiltration, however, the patient remained afebrile. His white blood cell count, which had been 12,000 on admission, ranged subsequently between 6,000 and 9,000, the differential showing a marked left shift. The patient developed periods of mental aberration; as exitus was impending he insisted on leaving the hospital and he was discharged on March 6, 1950. He died at home the following day.

### CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: Dr. Anthony, would you care to make any comments in regard to the chest films?

DR. DALLAS D. ANTHONY: We have reviewed the various films which were taken during this patient's many hospital admissions. Early in 1949 the cardiac silhouette was normal in size and the lung fields were clear. There was no change until December, 1949, when the patient was admitted for the sixth time. On that occasion his heart was increased in size but the lung fields were still clear. (Fig. 1.) At the time of his last admission on January 14, 1950, the cardiac enlargement had progressed even further than previously, and for the first time a flocculent infiltration was noted extending out from the right hilus. (Fig. 2.) By mid-February the infiltration had extended even further on the right side, had become coarser and had spread to involve the left side. The periphery of the lung fields remained clear but the cardiac enlargement was quite striking. (Fig. 3.)

DR. ALEXANDER: This patient was obviously suffering from chronic glomerulonephritis. He was studied in the hospital and in the Hypertension and Hematology Clinics quite intensively over a period of two years and I believe it is proper to point out that he was most cooperative during the entire period of his illness. Despite the fact that he suffered from the many symptoms enumerated in the protocol, he very willingly



2 3

FIG. 2. Chest film taken at the time of the patient's last admission showing progressive cardiac enlargement and flocculent infiltration extending out from the right hilum.

FIG. 3. Chest film taken later in the course of the last admission. The heart is even larger in size than it was previously and the infiltration in the parenchyma of the lung has extended to involve the left side as well as the right.

allowed the various investigations which will be discussed to go forward; although they constituted no undue risk to him, he knew full well that probably he would not be helped by any of the data so obtained but that others who followed him conceivably might be. Such an attitude certainly deserves the admiration and gratitude of physicians.

This case affords us an opportunity to consider many aspects of this important disease, particularly in its latter course. According to the history the patient had an episode of rheumatic fever which was followed soon thereafter by the passage of rust-colored urine. Rust-colored urine is a rather characteristic sign at the onset of acute glomerulonephritis and it is probably fair to assume that the patient had his first episode of acute nephritis at that time. We may also consider the relationship between acute glomerulonephritis and rheumatic fever. Dr. Glaser, could you comment on this particular question and on other phases of this subject?

DR. ROBERT J. GLASER: There are certainly similarities between acute glomerulonephritis and rheumatic fever. Both are considered by many investigators to represent diseases of hypersensitivity; that is, they are thought to result from a combination of antigen and antibody although the nature of the reaction and of its components remains to be elucidated. Both diseases bear relation to infection with group A beta-hemolytic streptococci although the relationship between acute rheumatic fever and preceding streptococcal infection is more clear-cut than is the case in acute glomerulonephritis. Thus it is probably fair to say that every patient who gets acute rheumatic fever has had a preceding infection with group A beta-hemolytic streptococci. The statistics are not quite as pronounced with glomerulonephritis although probably somewhere between 80 and 90 per cent of the patients who develop acute glomerulonephritis have preceding group A beta-hemolytic streptococcal infection. It seems clear that acute glomerulonephritis may follow infection with other organisms. For example, skin infections, particularly

with staphylococci, may precipitate an attack of acute glomerulonephritis.

There are certain similarities and certain differences between these two diseases and I shall mention only a few. Most of these comments will be generalizations and it should be remembered that considerable variation in the statistics in regard to certain of these points may be found. By and large the age incidence of both diseases is the same. Perhaps acute glomerulonephritis may occur somewhat more commonly before the age of three, and it is perhaps a little more frequent in young adults than is acute rheumatic fever. The sex incidence is very interesting. Rheumatic fever occurs essentially equally in males and females except for chorea which is more common in females. On the other hand, glomerulonephritis is consistently more common in males, occurring two to three times as often. The explanation of this interesting fact is not clear. In regard to the preceding streptococcal infection Seegal believes there is a difference in the type of infection which precedes each disease. He suggests that rheumatic fever more commonly follows superficial infections such as pharyngitis, whereas glomerulonephritis follows more deep-seated infections such as tonsillar abscess, cervical adenitis, etc.

Second attacks are very common in rheumatic fever and relatively rare in acute glomerulonephritis. For example, twenty patients, whom Seegal studied very carefully at the time of their first attacks of glomerulonephritis, recovered completely and subsequently all had a second streptococcal infection. Eighteen of these twenty patients showed no flare-up or manifestation of renal disease; at the time of the second infection two developed hematuria without albuminuria but in both of these instances there was no evidence of residual damage. The difference here between glomerulonephritis and rheumatic fever is striking since, if twenty rheumatics were exposed to a second attack of streptococcal infection, a fair number would be expected to have a second attack of rheumatic fever. In regard to familial incidence rheumatic fever differs from glomerulonephritis. May Wilson has pointed out that the incidence of acute rheumatic fever in families with a positive rheumatic history is significantly higher than in families in which there is no rheumatic history. Thus in one small series 100 per cent of the offspring of three marriages in which both mother and father had had rheumatic fever were afflicted with rheumatic fever. Although there are some instances in which glomerulonephritis occurs in several members of the same family, familial factors seem much less striking. Finally rheumatic fever is identifiable with a high incidence of residual damage and the problem of acute rheumatic fever is primarily that of its late effects. Acute rheumatic fever has a mortality of from 1 to 2 per cent but it is the chronic valvular disease following acute rheumatic fever which gives rise to the real problem in this disease. In acute glomerulonephritis, on the other hand, probably 85 to 90 per cent of the patients recover and most of them are quite resistant to second attacks. That group has a normal life expectancy.

In regard to the occurrence of both acute rheumatic fever and acute glomerulonephritis in the same patient it seems that this combination occurs in a very small percentage of patients. Various authors quote the incidence as about 1 to 2 per cent. Baehr studied 235 patients with either acute or chronic rheumatic heart disease at autopsy. Only two of these patients had pathologic evidence of glomerulonephritis.

DR. ALEXANDER: Since both rheumatic fever and glomerulonephritis occur after beta hemolytic streptococcal infection, is there any explanation of why one disease occurs in one instance and the other in the other?

DR. CARL G. HARFORD: One would predict, *a priori*, that the two should occur more commonly in the same patient; I cannot explain the fact that they do not.

DR. ALEXANDER: Dr. Wood, do you believe that the different strains of group A organisms may be important?

DR. W. BARRY WOOD, JR.: No, I do not think that there is any evidence that suggests that specific strains of group A streptococci are more apt to produce rheumatic fever than glomerulonephritis or vice versa. I do believe that Seegal's observation in regard to the type of infection, which Dr. Glaser has just mentioned, may be important. In addition to the fact that nephritis is apt to develop after deeper infection, it is worth noting that when nephritics get second attacks the latent period between the infection and the appearance of the symptoms and signs is extremely brief. In other words, the latent period becomes very short. In recurrent attacks of rheumatic fever the latent period usually is not shortened; thus second or even third attacks usually follow a latent period of seven to fourteen days. Perhaps when more is known of the pathogenesis of these diseases, an explanation for this interesting contrast may be apparent.

DR. ALEXANDER: Dr. Harford, would you tell us something about the immune mechanism which may be involved here?

DR. HARFORD: The pathogenesis of acute nephritis is by no means clear but certain concepts have attracted much interest recently. These are based on the postulate that auto-antibodies may develop; that is, that normal kidneys may be rendered antigenic as a result of bacterial infection; the mechanism of this process is not known. In experimental animals homologous kidney antibody has been produced by immunization of animals with combinations of kidney tissue and streptococcal or staphylococcal toxins. Considerable variation in results, however, has been encountered and the work of certain investigators has not been confirmed. If one uses heterologous systems, that is, if one makes anti-rat kidney antiserum in a rabbit, that serum introduced into the rat produces a lesion suggestive of glomerulonephritis. Furthermore it has been shown that if anti-rat kidney rabbit sera are iodinated with radioactive iodine and then injected into the rat, the antibodies are localized chiefly in the glomeruli.

DR. ALEXANDER: Thank you, Dr. Harford. Let us now consider the profound anemia which this patient exhibited. Dr. Loge has spent the past two years in Dr. Moore's laboratory studying the anemia of chronic nephritis. Dr. Loge, would you comment on this problem and on your studies?

DR. J. PHILIP LOGE: The anemia which is associated with renal insufficiency is usually normochromic and normocytic; occasionally it may be macrocytic and occasionally microcytic. It is fair to say at the outset that the pathogenesis of the anemia of nephritis is not completely understood. It has been generally assumed that the basic defect is insufficient production of red cells. Most writers have not considered that either blood loss or increased hemolysis plays a significant role. Thus in order to characterize further the anemia of renal insufficiency, we first interested ourselves in obtaining information regarding red cell production in patients with uremia. Such data can at present best be gotten by employing the radioactive iron utilization technic. For instance, if a given amount of radioactive iron is injected intravenously into a normal individual, 60 to 70 per cent of the iron is incorporated into red cells as hemoglobin in eight to ten days. In patients with renal insufficiency, on the other hand, radioactive iron so injected is used very poorly. We have now studied about ten uremics and all have utilized intravenously injected radioactive iron poorly; these observations indicate that there is a depression of erythropoiesis in patients with uremia.

In order to study the possibility that there might also be a hemolytic factor operating, a consideration suggested by the rapidity with which these patients sometimes become anemic, we have utilized the Ashby technic of differential agglutination. Using this technic in patients with the anemia of renal insufficiency, it has been found that in those patients whose anemia was rather stable, normal transfused red cells have the normal expected survival time in peripheral blood; conversely the red cells of such patients survive normally in normal recipients. In four

patients, however, the survival times were extremely short, ranging between forty to sixty days in contrast to a normal survival time of 120 days. This finding suggests that at certain times a hemolytic factor operates. Furthermore, when cells from one of these four patients with chronic renal insufficiency and azotemia were transfused into a normal person, the cells survived a normal period, that is, 120 days. Thus, the hemolytic factor may be said to be extracorpuscular. Such patients with a hemolytic component to their anemia—and the patient whose case is being considered today was one—differed from the others in that they became rapidly and progressively more anemic; all were in the terminal phase of their disease.

DR. ALEXANDER: Thank you Dr. Loge. The patient was also studied by the Hypertension Division. Dr. Schroeder, you transfused blood from hypertensive and normotensive persons into this patient. Would you tell us something of the experiment and the inferences which you drew from the studies?

DR. HENRY A. SCHROEDER: We have been interested in pressor substances in hypertensive blood. In addition to attempting to identify and characterize such pressor substances chemically, we have used an indirect method for detecting pressor substances in hypertensive blood, employing the kidney as the test object.[1] We postulated that if hypertensive blood which was transfused contained pressor substances, these substances might constrict the efferent arterioles of the normal kidney and might lead to transient hypertension. Clearances were therefore determined as arterial blood was transfused. We found that in normal patients there was no effect whatsoever, and in patients with mild hypertension the transfusion of hypertensive blood led to little or no change in blood pressure or renal hemodynamics. When, however, patients with severe renal disease were transfused with hypertensive blood, their blood pressures rose to higher levels than prior to transfusion. In this patient for example the average diastolic pressure during the experiment was about 25 mm. of mercury higher than that recorded before transfusion.

DR. ALEXANDER: How long did the blood pressure remain elevated?

DR. SCHROEDER: About one and one-half hours.

DR. ALEXANDER: This patient had the dramatic procedure of exchange transfusion performed on one occasion. Dr. Loeb, would you discuss this study?

DR. VIRGIL LOEB, JR.: Blood is introduced into one of the veins of the arm and is removed from the opposite arm so that the volume remains constant. Various modifications include the use of catheters and two-way pumps. Figures available on the volume of blood necessary to carry out a satisfactory exanguino-transfusion are interesting. The injection and removal of 5 L. of blood affords approximately 60 per cent replacement while 15 L. are required for 95 per cent exchange. Although the procedure was first used in the treatment of erythroblastosis fetalis, as advocated by Wiener, Diamond and others, the first extensive series of replacement transfusions in other diseases was published by Bessis, the director of the Paris Blood Transfusion Center, about a year ago.[2] He advocated the use of the procedure in patients with acute leukemia, based on the postulate that normal persons have an antileukemic substance in their blood. His results in thirty-eight cases are interesting but difficult to evaluate. We have performed replacement transfusion in one patient with acute leukemia, removing and replacing 10 L. of blood in four hours without great difficulty but without obvious beneficial effect to the patient. The rationale in using the procedure in renal insufficiency is based on the premise that "toxic products" can be removed; during the interval in which the blood electrolytes are normal or rela-

[1] GOLDMAN, M. L., KRISS, J. P., FUTCHER, P. H. and SCHROEDER, H. A. The transfusion of arterial hypertensive and normotensive blood into hypertensive subjects. *Am. J. M. Sc.*, 217: 637, 1949.

[2] BESSIS, M. The use of replacement transfusion in diseases other than hemolytic disease of the newborn. *Blood*, 4: 324, 1949.

tively normal, the kidneys may be able to recover their excretory function. Of course, this method would find its most logical application in cases of acute nephritis or lower nephron nephrosis in which the pathologic lesion is probably reversible. In cases of azotemia an attempt is made to lower the blood non-protein nitrogen by utilizing the replacement transfusion as a type of artificial kidney. Although transient decrease in the non-protein nitrogen may follow the use of the procedure, it is important to realize that the tissues become saturated with retained nitrogenous products, and it would be necessary to carry out multiple replacement transfusions before any significant lowering of the blood urea could be anticipated.

DR. ALEXANDER: There is one other feature of this case which is most interesting, namely, the pulmonary infiltration. Dr. Tillman, as you followed this patient on the ward what was your impression of the pulmonary changes?

DR. A. CLIFFORD TILLMAN: It is not at all uncommon today for the radiologist, after he views a chest film, to call the clinician to inquire as to the non-protein nitrogen level in the patient's blood. Actually the pulmonary changes concomitant with uremia have been studied chiefly by the radiologists. When the pulmonary infiltration was first noted, some of us believed that the changes might have represented so-called uremic pneumonia; we were, however, all disturbed by the fact that the lesion was localized to one side. As the lesion progressed without any clinical signs or symptoms of bacterial pneumonia we became more and more impressed with the probability that it was due to uremia. Finally when it extended into the other lung, we became convinced. This patient lived longer with these changes than any other I have seen. The pathologic picture is somewhat confused. I have seen only a few pathologic sections of uremic pneumonia; the changes were those of interstitial non-specific infiltration. The only alveolar change was the presence of a hyaline-like membrane such as ones sees in interstitial pneumonia within the alveoli. Usually patients die within a week or ten days after the pulmonary manifestations appear.

DR. ALEXANDER: Did the patient ever cough up bright red blood?

DR. TILLMAN: He had a cough which became increasingly severe and he had some blood in his sputum, but at the same time he had many nose bleeds and we believed that the blood in his sputum probably came from his nose.

DR. ALEXANDER: In summary, as at the outset, I believe there is no question that this patient had chronic glomerulonephritis. I would predict, therefore, that he will have the very small kidneys typical of chronic glomerulonephritis and a large heart. Probably he also will have signs of uremic pericarditis. Are there any other comments?

DR. SCHROEDER: I think it is interesting to point out that when we studied this patient in April, 1948, his renal plasma flow was only 20 cc. per minute, less than 5 per cent of normal. That value was noted two years before the patient died.

*Clinical Diagnosis:* Chronic glomerulonephritis.

### PATHOLOGIC DISCUSSION

DR. JAMES C. HAWKINS: There was pitting edema of the subcutaneous tissues, most marked in the lower extremities and hands. Clear, straw-colored fluid was present in all serous cavities. There were 1,000 cc. in the pericardial sac. The heart was enlarged, weighing 900 gm. The epicardium was thick and covered with a layer of fibrin. The mitral valve was slightly thickened but not deformed. There were petechiae in the anterior leaflet. The coronary arteries and myocardium were not grossly remarkable.

The lungs were heavy and moist. In the perihilar areas the parenchyma was particularly firm and slightly nodular bilaterally. The gross architecture of the cut surfaces was not recognizably altered except for the evidences of chronic congestion and edema. A caseous nodule was present in the lower

lobe of the left lung. The kidneys were about normal in weight. Their capsules stripped easily and a finely granular, pale surface with no petechiae was exposed. On the cut surface the glomeruli were prominent small grey elevations. The corticomedullary junction was obscure but the cortex was not thin. There were petechiae in the pelvic mucosa. The liver weighed 2,610 gm. and was remarkable only for its congested appearance. The spleen was firm and weighed 560 gm.; the cut surface was dark red and did not retract from the capsule. Petechiae and ecchymoses were present in the mucosa of the ileum and colon. The bone marrow of the sternum, ribs, lumbar vertebrae and the proximal part of the left femur was pale but not fatty.

DR. DAVID E. SMITH: The gross observations gave evidence of chronic renal disease terminating with uremia and complicated by cardiac failure. Hypertension had undoubtedly existed for some time as evidenced by the fact that the heart was hypertrophied in the absence of either valvular or arterial lesions. The chronic congestive changes in various viscera and the anasarca, in contrast to the kidneys of almost normal size, suggested that the cardiac failure was a particularly significant cause of many of the features of this case.

The first photomicrograph (Fig. 4) is of a section of the kidney. It shows that there was a decrease in the total amount of parenchyma as there were five glomeruli in this very restricted field. Each glomerulus was affected to some extent by a process that in one instance had led to almost complete scarring of the glomerulus and in others to fibrous thickening about Bowman's capsule with thickening of the epithelium over the glomerular tufts and lining of the capsule. Distinct lobulation of the glomerular tufts was present and in one glomerulus the epithelial proliferation had obliterated the tuft and formed complete adhesions to the capsule. Essentially the same changes were present throughout all sections of the kidneys despite the fact they were not appreciably decreased in size. There was, therefore, evidence of glomerulonephritis of years' duration, yet still with some proliferative reaction. The cortical scarring was sufficiently extensive to be compatible with Dr. Schroeder's estimates of the degree of this patient's renal damage.

In patients with long-standing uremia there is often a change in the pancreas which consists of dilatation of the acini and small ducts. Figure 5 indicates that this lesion is not constant; it was not present in this case.

There was fibrosis and hyalinization of some of the vascular walls, but these changes were related to the existence of hypertension. Figure 6 is of a section of vertebral bone marrow. Grossly the bone marrow was investigated in the femur, as well as the usual sites, and was found to be red. There was, therefore, an extension of the amount of hematopoietic marrow in this man's bones; however, the sections show that actually there was hypoplasia. The volume of the marrow cavity occupied by the loose hematopoietic tissue was only a small percentage of that usually occupied in a normal young adult. There were also foci of granular precipitate such as is often present in hypoplastic marrow after toxic damage. Most of the myeloid cells that persisted were members of the granulocytic series.

Figure 7 illustrates a section of myocardium in which there were many Aschoff nodules. These nodules were slightly atypical in that there was not much fibrinoid or very many Anitschkow cells, and most of the nodules were present in the region just under the endocardium. They were too distinct, however, to be a non-specific reaction, and they indicated that this man had a rheumatic lesion of his myocardium at the time he died. Grossly, there was very little evidence that he had an earlier myocarditis or endocarditis of significant degree; however, here in the terminal episode he showed definite acute myocarditis that was reasonably severe. Sections of the mitral valve contained a little perivascular infiltration and fibrous thickening of the leaflet which were interpreted as the only evidences of earlier endocarditis.

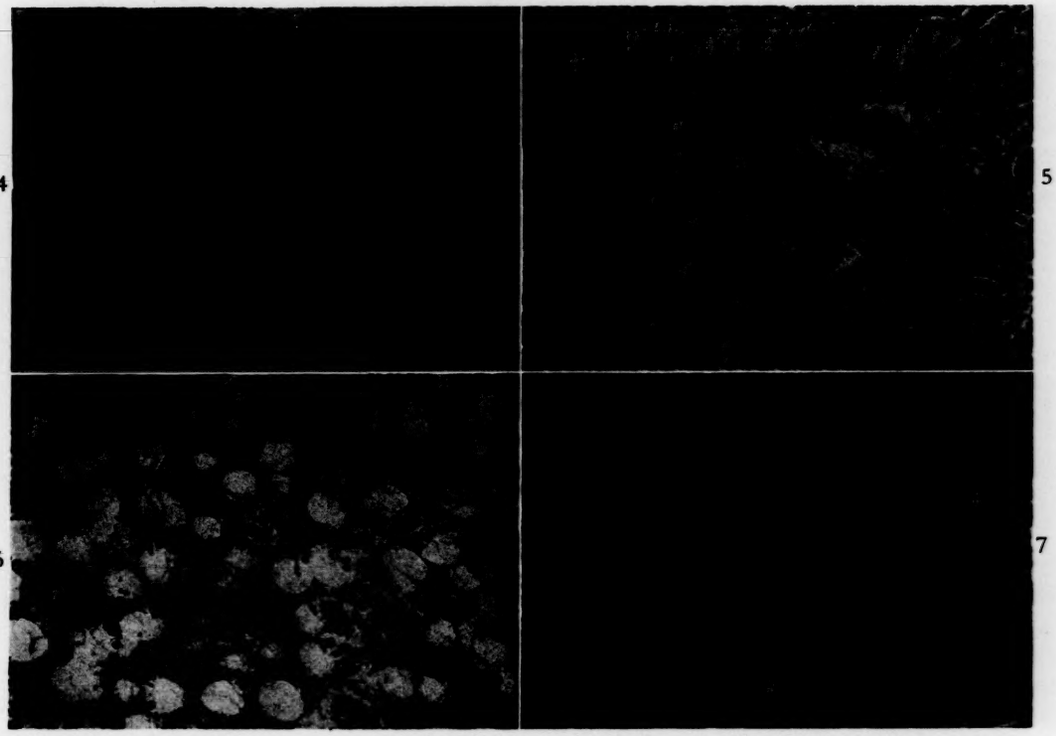



FIG. 4. Interstitial scarring in the cortex of the kidney and proliferative and fibrous changes in the glomeruli. In the glomerulus at the right margin Bowman's space is obliterated by proliferation of capsular epithelium and pericapsular fibrosis.
FIG. 5. Hyalinization of the arteriolar walls in the pancreas: a lesion related to the presence of hypertension. The pancreatic parenchyma does not show the dilatation of ducts and acini often present in chronic uremia.
FIG. 6. Hypoplasia of the hematopoietic elements in the vertebral bone marrow and a granular interstitial precipitate suggestive of progressive toxic damage.
FIG. 7. A slightly atypical Aschoff nodule in the myocardium. Although there is fibrinoid degeneration in this nodule, well developed Anitschkow myocytes cannot be identified. Other nodules contained the myocytes but did not exhibit fibrinoid degeneration of collagen.

The lungs were particularly investigated histologically to determine the nature of the lesions discovered by the radiologists. In Figure 8, which is from a focus in the middle lobe of the right lung, the alveoli were filled with macrophages that contained granules of hemosiderin. There was also a diffuse increase in fibrous tissue in the interlobular septa and proliferation of the alveolar epithelium. These are the changes of chronic passive congestion of the lung with perhaps a little chronic inflammation to account for the epithelial proliferation. Throughout the sections taken from the perihilar regions of the lung there were small lesions like that illustrated in Figure 9. These were masses of fibroblasts that had grown into the alveoli and were like those seen in organized pneumonia. The curious thing about these lesions was their sparse and scattered distribution. There were rarely more than two organized alveoli in a single low power microscopic field. Accompanying them were fat-filled macrophages that were probably remnants of the resolution of the pneumonia that gave rise to the organized exudate in the alveoli. Figure 10 illustrates the fibrous organization extending into a small bronchus which suggested that the primary lesion was in the terminal bronchi and the organization extended into the alveoli rather than arising there. Descriptions by others of "uremic pneumonia" from a morphologic viewpoint could not be found and no one seems to have had sufficient experience with this diagnosis to say whether the lesions are often, or ever, like those in this case. Figure 11 is from the nodule found

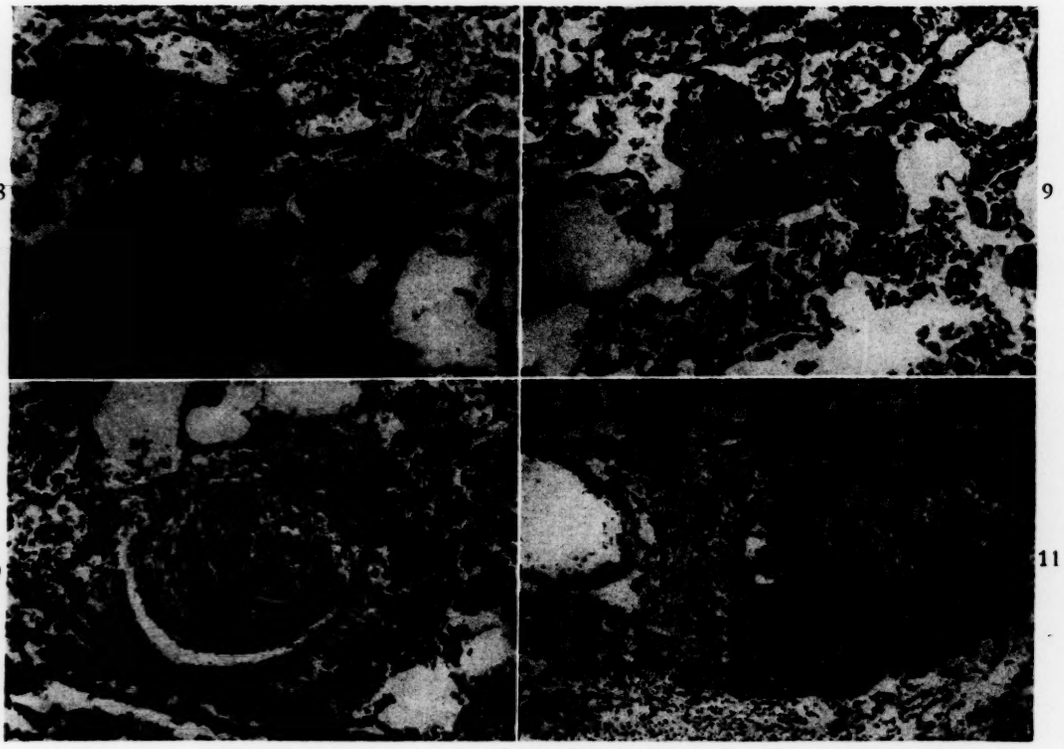



FIG. 8. Fibrosis, alveolar epithelial proliferation and hemosiderin-filled macrophages in the middle lobe of the right lung. These are essentially the changes of chronic passive congestion.
FIG. 9. Organized exudate in two alveoli from the perihilar regions of the lung. The isolation of these lesions is in contrast to the larger masses of adjacent organized alveoli in the usual type of organized pneumonia.
FIG. 10. Organized exudate in a terminal bronchiole from the area diagnosed clinically as uremic pneumonia.
FIG. 11. Tubercle from the base of the lower lobe of the left lung.

in the lower lobe of the left lung. It was a typical tubercle and accounted for the presence of chronic pleurisy at the site reported in the clinical history.

The anatomic evidence, in summary, indicated that this man had subacute and chronic glomerulonephritis. He developed hypertension which resulted in hypertrophy of the heart, and then terminally he had an exacerbation of rheumatic myocarditis. The terminal picture was complicated by physiologic failure both of the cardiovascular system as well as the kidneys. The lungs contained a peculiar focal organized pneumonia in the perihilar regions where "uremic pneumonia" had been recognized by the clinicians.

Only a very small amount of hemosiderin was present in the spleen despite the history of transfusions and the condition of the bone marrow. The brain was sectioned and showed no gross lesions, but microscopically there were a few granules of hemosiderin and macrophages around subcortical blood vessels which may have been related to damage inflicted by the convulsions mentioned in the patient's history. There were no pulmonary emboli or coronary occlusion to explain this patient's rather sudden demise; however, the enlarged heart and 1,100 cc. of fluid in the pericardial sac probably had a great deal to do with providing the physiologic imbalance leading to that event.

*Final Anatomic Diagnoses:* Subacute and chronic glomerulonephritis; hypertrophy and dilatation of the heart; Aschoff nodules in the myocardium; chronic passive congestion of the lungs, liver and spleen; focal organized pneumonia in the perihilar regions of the lungs; anasarca.

*Acknowledgment:* Illustrations were made by the Department of Illustration, Washington University School of Medicine.

# Special Feature

## American Federation for Clinical Research

ABSTRACTS OF PAPERS PRESENTED AT THE SOUTHERN SECTIONAL MEETING IN NEW ORLEANS, MARCH 17, 1950

EFFECT OF FEVER ON POSTCLYSIS GLYCOSURIA. *Walter L. Bloom, M.D., Harold Sutker, M.D. and William B. Fackler, Jr., M.D. Atlanta, Ga.* (From the Medical Service, Lawson V. A. Hospital, and the Department of Biochemistry, Emory University Medical School.)

Clinical observation has suggested that the degree of postclysis glycosuria is increased during fever. To test the validity of this impression, fasting concentrations of blood and urine reducing substance were studied in ten normal and in twelve febrile patients. When 2,000 cc. of 5 per cent glucose were given intravenously in two hours, the peak of hyperglycemia was higher and the quantity of urinary glucose was greater in the febrile patients. The differences in blood sugar levels in the two groups were small, however, while the differences in quantity of sugar excreted were great. Therefore, the additional possibility of altered renal factors was investigated. Blood and urine sugars and also renal clearance studies were done on another group of febrile patients. A duplicate procedure was followed in repeating the determinations after an afebrile interval. In each patient the mean blood sugar level, renal blood flow and glomerular filtration rate were higher during fever.

It is concluded that greater hyperglycemia and increased glomerular filtration rate during the febrile state contribute to the presentation of more glucose to the renal tubules with a consequent increase in postclysis glycosuria.

ADRENAL CORTICAL FUNCTION IN ESSENTIAL HYPERTENSION; STUDY OF THE EOSINOPHIL RESPONSE TO EPINEPHRINE. *Harold Joseph, M.D., John Binion, M.D. and Louis Tobian, Jr., M.D.* (*Introduced by Alfred W. Harris, M.D.*) *Dallas, Tex.* (From the Department of Medicine, Southwestern Medical College.)

In normotensive and hypertensive individuals eosinophil levels were determined just before and four hours after a subcutaneous injection of .002 mg. of epinephrine per pound of body weight. In the group of twenty-six normotensives (average blood pressure 119/73 mm. Hg) the average eosinophil decrease was 56 per cent. In the group of thirty hypertensives (average blood pressure 196/113 mm. Hg) the average eosinophil drop was 57 per cent. This slight difference is not significant. These results indicate that the anterior pituitary-adrenal cortex mechanism in patients with essential hypertension has a normal sensitivity to injected epinephrine and probably also to endogenously secreted epinephrine.

ADRENAL ACTIVITY IN THYROID DYSFUNCTION; PRELIMINARY REPORT. *Arthur J. Moseley, M.D., Francis W. Fitzhugh, Jr., M.D., D. James Hughes, M.D. and Arthur J. Merrill, M.D. Atlanta, Ga.* (From the Medical Service, Grady Memorial Hospital, and Department of Medicine, Emory University School of Medicine.)

The total eosinophile count and sweat sodium concentration were utilized as indicators of 11-oxy and DOCA-like activity, respectively, of the adrenal cortex. In thirty-seven normal subjects the average sweat sodium was 45.4 mEq./L. (range: 11.5 to 82.2 mEq./L). In thirty-two patients with thyrotoxicosis the average sweat sodium concentration was 27.1 mEq./L. (range: 3.9 to 124 mEq./L.). Using 18 mEq./L. as the lower limit of normal it was found that 44 per cent of the thyrotoxic patients had a low sweat sodium concentration. Patients with moderate elevation of the basal metabolic rate and without heart failure tended to have a very low sweat sodium concentration. With a basal metabolic rate above 50 or with the presence of heart failure, the sweat sodium concentration was normal in all but two patients. Four patients with spontaneous and two with postoperative myxedema had a mean sweat sodium of 74.8 mEq./L.

Eleven of fifteen thyrotoxic patients had

eosinophile counts above 90 per cu. mm. Of these eleven thyrotoxic patients with normal eosinophile counts six had low and five had normal sweat sodium concentrations. Only one of the four patients with the low eosinophile count had a low sweat sodium concentration. This lack of correlation between sweat sodium concentration and eosinophile count is further evidence that the adrenal cortical hormones do not respond to ACTH as a unit.

The implications of these findings and a tentative mechanism for the low sweat sodium concentration in thyrotoxicosis will be discussed.

MECHANISM OF RESPONSE TO INSULIN-INDUCED HYPOGLYCEMIA IN MAN. *Philip K. Bondy, M.D., Atlanta, Ga.* (From the Department of Medicine, Emory University School of Medicine.)

The role of the liver in correcting the hypoglycemia resulting from administration of insulin to normal human subjects was studied using the hepatic venous catheter technic. Ten minutes after insulin (0.1 unit of Lilly insulin without glycogenolytic factor/kg. intravenously) glucose is retained by the liver. At twenty and thirty minutes the liver releases small amounts of glucose insufficient to halt the downward course of the dextrose curve. By forty minutes the glucose concentration has reached its nadir and the downward trend is reversed as increased amounts of glucose pour into the hepatic vein, presumably in response to epinephrine. The mechanism of the adrenal medullary response was studied by performing insulin tolerance tests on normal subjects with and without tetraethylammonium chloride (TEACl), 5 mg./kg. intravenously. Sympathetic blockade did not affect the glucose curve for thirty minutes; however, in each subject the glucose concentration after TEACl was lower than the control at forty minutes, suggesting that inhibition of preganglionic synapses to the adrenal medulla decreases the ability to respond to hypoglycemia. The adrenal medullary response to hypoglycemia therefore probably results from impulses arising in the central nervous system and not from direct stimulation of the medulla by reduced blood glucose concentration.

GLUCOSE TOLERANCE; COMPARISON OF FOUR DIFFERENT TYPES OF TESTS. *John H. Moyer, M.D. Houston, Tex. and C. Ray Womack, M.D. Nashville, Tenn.* (From the Department of Medicine, Baylor University School of Medicine, and Vanderbilt University School of Medicine.)

Discrepancies are frequently noted when different technics are employed for the evaluation of glucose tolerance. Therefore, four different types of glucose tolerance tests in common use today were carried out on a control group of 100 subjects in order to establish normal values. The specificity of the individual tests was then evaluated. Similar studies, using for interpretation the values obtained in the control group, were performed on twenty-six diabetic patients.

The results revealed that the one-hour, two-dose test (Exton-Rose) is overly sensitive and of little diagnostic value. The intravenous test and the one-dose oral standard test are most valid for clinical use, the intravenous being somewhat less specific than the standard. In both, the maximum blood sugar concentration was found to be of no diagnostic value *per se* whereas the blood sugar concentration two hours after the administration of glucose was critical. The postprandial test is of value for preliminary purposes.

EFFECT OF CARINAMIDE ON BLOOD CONCENTRATION OF AUREOMYCIN. *J. M. Rumball, M.D., Murray Sanders, M.D., Clark Rodman, M.D., Gonzalez Suret, D.V.M. and Benjamin Akin, M.D. Coral Gables, Fla.* (From the University of Miami Research Unit at Veterans Administration Hospital.)

It has been shown that the blood concentration of penicillin can be enhanced by oral administration of carinamide (4-carboxyphenylmethansulfonamide). It was suggested that carinamide also enhances the blood concentration of aureomycin, by the work done by the authors and work reported elsewhere.

Method: (1) Volunteers were given 500 mg. of aureomycin every six hours, and blood determinations were made on the second day every four hours. This same procedure was repeated a week later on the same volunteers but in addition they were given an initial dose of 4 gm. of carinamide followed by 2 gm. every two hours during that day. (2) Urinary excretion studies were made on selected volunteers.

Results: (1) The blood concentration appears to be slightly enhanced but not sufficiently to be of clinical value. (2) The urinary excretion is diminished by the use of carinamide. (3) Com-

ments are made regarding the mechanism involved.

ABSCESSES IN THE VALVE RINGS OF THE HEART; A FREQUENT AND NOT WELL RECOGNIZED COMPLICATION OF ACUTE BACTERIAL ENDOCARDITIS. *Walter H. Sheldon, M.D. and Abner Golden, M.D. Atlanta, Ga.* (From the Department of Pathology, Emory University School of Medicine and Grady Memorial Hospital.)

Since 1947 we have observed ten patients with acute bacterial endocarditis who at autopsy showed one or more abscesses in the valve rings of the heart. The abscesses measured from 1 to several cm. in size and involved most commonly the aortic valve ring although the other rings were not spared. The infection was caused by pneumococci in nine patients. Of these, eight had pneumonia, meningitis or both. The same organism was obtained before and after death in three of these patients. Staphylococcus aureus was cultured before and after death from another patient with septic abortion. Syphilitic aortitis was present in six patients. Evidence of rheumatic heart disease was lacking.

All patients had received penicillin over periods ranging from three to twenty-seven days in total amounts from 600,000 to 69,000,000 units.

We believe that these abscesses are now seen more frequently although some may have been overlooked in the past. Their structure suggests an embolic origin similar to septic emboli elsewhere. Since the valvular and other lesions generally showed advanced healing, it is possible that penicillin does not sufficiently penetrate the valve ring and that the abscesses act as a source of persistent infection.

AN EVALUATION OF THE HEMAGGLUTINATION TEST IN TUBERCULOSIS, SARCOIDOSIS AND NON-TUBERCULOUS PULMONARY INFECTIONS. *Martin M. Cummings, M.D., Ernest H. Runyon, Ph.D. (by invitation) and Jack W. Fleming, M.D. (by invitation) Atlanta, Ga.* (From the Medical Research Laboratory, Lawson V.A. Hospital and Department of Medicine, Emory University School of Medicine.)

A hemagglutination test devised by Dubos has been employed for the demonstration of antibodies to the products of tubercle bacilli in human sera obtained from normal tuberculin-negative individuals, normal tuberculin-positive reactors, patients with active cases of tuberculosis, BCG-vaccinated individuals and patients with pulmonary diseases such as sarcoidosis and pulmonary mycoses.

An attempt is made to correlate the hemagglutination test with the clinical activity of tuberculous patients and with the immunologic status of these individuals. Evidence is presented which suggests that allergy and immunity are separate phenomena in tuberculosis. Further evidence indicates that sarcoidosis is not related to tuberculosis immunologically. Interesting data are presented from small groups of individuals vaccinated with BCG, some of whom have reverted to tuberculin negativity while still maintaining a fairly high titer of agglutinating antibodies. The clinical significance of the hemagglutination test is discussed.

ANGIOCARDIOGRAPHY UTILIZING A PHOTOFLUOROGRAPHIC TECHNIC. *Harold Jacobs, M.D. (by invitation), Louis Levy II, M.D., Harold Chastant, M.D. (by invitation) and Howard Strauss, M.D. (by invitation). New Orleans, La.*

Angiocardiograms have been taken by utilizing a photofluorographic unit with a Fairchild 70 mm. camera with an Eastman Fluoro Ektar F:1.5 lens, Patterson type B-2 screen, and a Dynamax 25 tube. The patient can be placed in a horizontal or vertical position, and fifteen to eighteen exposures are made in sixteen to twenty seconds at 200 MA and 85 KVP on 70 mm. green sensitivity film. Twelve representative cases are presented demonstrating the usefulness of angiocardiography in the diagnosis of aneurysms involving various regions of the aorta, congenital heart disease, mediastinal masses and pulmonary disease.

STUDY OF THE SPATIAL VECTORCARDIOGRAM IN LEFT BUNDLE BRANCH BLOCK. *J. A. Abildskov, M.D., J. Frank Pantridge, M.D. (by invitation) and G. E. Burch, M.D. New Orleans, La.* (From the School of Medicine, Tulane University of Louisiana.)

The difficulty of determining electrocardiographically the extent of lesions associated with left bundle branch block prompted study of its spatial vectorcardiogram. Projections of the vectorcardiogram on various planes of the equilateral tetrahedron reference system were photographed and used to construct wire models representing the QRS sÊ-loops. Twenty-

eight subjects whose electrocardiograms had been interpreted as indicating left bundle branch block were studied and divided into four groups on the basis of similar QRS sÊ-loops.

Eight subjects presented QRS sÊ-loops with smooth oval contours tending to enclose single plane areas whose axes were directed posteriorly and to the left. This pattern resembled that of subjects with marked left ventricular hypertrophy. The QRS sÊ-loops of six subjects enclosed narrow irregular areas. Five showed advanced congestive failure suggesting this pattern to be consequent to gross diffuse myocardial damage. The QRS sÊ-loops of eleven subjects were characterized by local irregularities as might be expected if a local muscle mass were destroyed. Three subjects with minimal clinical evidence of heart disease presented QRS sÊ-loops resembling those of normal subjects. A local lesion interrupting the bundle branch might account for the block in these subjects.

RELATIVE AMOUNTS OF QUINIDINE LACTATE AND QUININE DIHYDROCHLORIDE REQUIRED TO PRODUCE COMPARABLE ELECTROCARDIOGRAPHIC CHANGES AFTER INTRAVENOUS ADMINISTRATION IN THE DOG. *Ross C. Kory, M.D., Richard France, M.D. and George R. Meneely, M.D. Nashville, Tenn.* (From the Research Laboratory of Thayer Veterans Administration Hospital and the Department of Medicine of Vanderbilt University School of Medicine.)

Since both quinidine and quinine are effective against certain arrhythmias and since a new readily soluble quinidine lactate preparation (Eli Lilly and Company) has become available, it is desirable to assess the relative intravenous effect of this drug with the more commonly used quinine dihydrochloride.

In eighty experiments 5 to 20 mg. per kg. of each preparation were diluted in 50 ml. of isotonic saline solution and administered intravenously over a six-minute period to dogs unanesthetized and under nembutal anesthesia. Electrocardiographic tracings were taken at one-minute intervals for ten minutes, at two-minute intervals for the next ten minutes and less frequently thereafter. Consistent and characteristic electrocardiographic changes were found with both drugs. These developed in the following order: (1) elevation of T wave, (2) depression of ST usually with development of a deep S wave, (3) widening of QRS and (4) with high dosage increase in duration of QT and PR. Rate changes were variable but most often showed an increase.

On the basis of this method quinidine lactate weight for weight was consistently only slightly more potent than quinine dihydrochloride, much less than the reported differences for the orally administered preparations.

TRANSFER OF RADIOACTIVE MERCURY ACROSS A MEMBRANE PRODUCED BY THE APPLICATION OF CANTHARIDES TO THE SKIN OF MAN. *Frank J. Kelly, M.D. (by invitation), Arthur H. Svedberg, M.D. (by invitation) and Vernon C. Harp, M.D. (by invitation), (Introduced by C. Thorpe Ray, M.D.) New Orleans, La.* (From the Department of Medicine, Tulane University School of Medicine and Charity Hospital of Louisiana, at New Orleans.)

Transfer of radiomercury across the base of blisters produced by application of cantharides to forearms of thirty-one subjects was observed during studies of pharmacologic properties of a mercurial diuretic, mercuhydrin.

The concentration-time course of radiomercury on both sides of this membrane was followed for four hours after intravenous injection of the labeled diuretic in fifteen cases. There was close agreement between the right and left forearms of the same individual. Considerable variation among different subjects was noted. No differences were observed between control subjects and those with congestive heart failure. Histamine applied locally enhanced the rate of transfer across this membrane. Benadryl did not inhibit this effect. Venous congestion inhibited the rate of transfer slightly. Epinephrine locally had no effect. Substitution of the patients' plasma for physiologic saline as the fluid bathing one side of the membrane did not alter the concentration-time course.

Radiomercury was added to fluid bathing the blister base in sixteen subjects and its rate of disappearance was followed for four hours. A simple exponential rate of disappearance was observed. Congestive heart failure, epinephrine and histamine did not influence results. Presence of plasma protein inhibited transfer of mercury. Normal skin was impermeable to mercury.

HEMATOLOGIC EFFECTS OF BONE MARROW METASTASES. *Ulfar Jonsson, M.D.* (*Intro-*

*duced by R. W. Rundles, M.D.) Durham, N.C.*

One hundred fifty-two patients with malignant tumors were studied regarding the feasibility of demonstrating tumor implants in bone marrow by aspiration technic, the hematologic effects of tumor growth and cause of the anemia frequently associated with neoplasm. Sites for marrow aspiration were selected by preference in areas of bone pain, tenderness, tumor growth and roentgen abnormality.

Tumor implants were demonstrated in seventy-one of 152 patients, with the highest frequency in those with carcinoma of the prostate or breast, in neuroblastoma and in those in whom the site of the primary tumor was not discovered. Anemia with evidence of marrow replacement occurred in highest percentage in patients with carcinoma of the prostate and neuroblastoma. Immature granulocytes and nucleated red blood cells appeared in these patients when the hemoglobin fell below 8.5 gm. per 100 cc. Plasma cell proliferation was prominent in six of seven patients with hypernephroma and occasionally in other tumors. Metastatic implants from mucus-producing carcinomas of the intestinal tract and neuroblastomas have cytologic features helpful in indicating the site of the primary tumor.

STUDIES OF THE SICKLING PHENOMENON. *William C. Levin, M.D. and Rose G. Schneider, Ph.D. (by invitation) Galveston, Tex.* (From the Department of Internal Medicine, Hematology Research Laboratory, Department of Neurology and Psychiatry and Tissue Culture Laboratory, University of Texas Medicine Branch.)

We have shown that erythrocytes susceptible to sickling contain about the same concentration of carbonic anhydrase as do non-susceptible erythrocytes; repeated washings do not appreciably alter the carbonic anhydrase content nor is the sickling capacity of repeatedly washed cells restored by the addition of concentrated carbonic anhydrase. We concluded that irreversible loss of sickling capacity is not associated with loss of carbonic anhydrase, as had been suggested by other investigators.

To determine the effect of mechanical factors on irreversible loss of sickling capacity, susceptible erythrocytes were shaken in a Kahn shaker for two hours and samples removed periodically. The ability of these erythrocytes to sickle was inversely proportional to the length of time they were shaken. Influences of mechanical factors were also studied by suspending susceptible cells in their own plasma and alternately centrifuging and resuspending in the plasma. After such treatment progressive loss of sickling ability occurred. It is concluded that mechanical agitation of susceptible erythrocytes decreases their ability to sickle.

Biochemical studies of sickling erythrocytes are also in progress. The absorption spectrum of oxyhemoglobin from individuals with the sickling tendency has been compared with that of normal individuals. No differences have been found between them, indicating that the heme component of oxyhemoglobin from sickling erythrocytes does not differ from the normal.

THE "L. E." CELL AND ITS DEMONSTRATION IN PERIPHERAL BLOOD. *Milton H. Freedman, M.D. (Introduced by Max Michael, Jr., M.D.) Chamblu, La.* (From the Medical Service, Lawson V. A. Hospital, the Medical Clinic, Grady Memorial Hospital, and the Department of Medicine, Emory Medical School.)

The diagnosis of acute disseminated lupus erythematosus may be facilitated by finding in the bone marrows of certain patients with this disease polymorphonuclear leukocytes containing basophilic homogeneous material. In addition polymorphonuclear leukocytes are occasionally seen clustered around masses of bluish staining material, forming rosettes. Others have reproduced this phenomenon by mixing oxalated plasma of patients with acute lupus and normal bone marrow cells.

We have examined heparinized peripheral blood in addition to heparinized bone marrow of three patients with this disease. In all instances the peripheral blood preparations showed typical "L. E." cells; only two of the three marrows did so. Control non-heparinized preparations of the marrow and peripheral blood of the patients failed to reveal this phenomenon. It is believed that heparin (or possibly other anticoagulants) is a necessary factor for the production of "L. E." cells. Although artefaction cannot be ruled out, the test appears to be peculiar to acute lupus and so remains a valuable diagnostic aid. The fact that peripheral blood may show these cells, thereby obviating bone marrow aspiration, makes it even more practical.

Further studies are necessary to elucidate the significance of this phenomenon.

COAGULATION TIME, ITS SENSITIVITY AND WHAT IT MEASURES. *George W. Allen, M.D. (by invitation) and Edgar Hull, M.D. (by invitation). (Introduced by John H. Seabury, M.D.) New Orleans, La.* (From the Department of Medicine of the Louisiana State University School of Medicine.)

The paper is concerned chiefly with the effect of extraneous influences such as temperature, calcium, thromboplastin and the "wettability" effect upon direct clotting time. It is believed that the failure of this type of test to measure tendencies of increased and decreased coagulability is due to its lack of sensitivity. It is also the opinion of the authors that the addition of calcium and thromboplastin in excess, as is done with the prothrombin time, is in large part responsible for the lack of exact correlation between the prothrombin and coagulation times. For example, it is shown that coagulation under ordinary circumstances does not operate at optimum calcium concentrations.

It is thought that the state of coagulability in the body does not maintain a constant level even when depressed, but varies with the stress and strain of conditions of the moment, and that the direct coagulation time is the best known measure of the summation of clotting power. Some suggestions for increasing the sensitivity and accuracy of the test are included.

EFFECTS OF VARIOUS MANIPULATIONS ON THE KIDNEY ON THE PATHOLOGIC APPEARANCE OF THE TISSUES IN THE DOG, WITH PARTICULAR REFERENCE TO CHANGES IN THE MYOCARDIUM AND BLOOD VESSELS. *Arthur Grollman, M.D., E. E. Muirhead, M.D. and James A. McLean, M.D. (by invitation). Dallas, Tex.* (From the Department of Experimental Medicine, Southwestern Medical School of the University of Texas.)

The following experiments were carried out in order to elucidate further the relationship between arteriolar necrosis, necrosis of the heart and other lesions of malignant hypertension to such factors as elevation of blood pressure and accumulation of catabolites to which they are usually attributed. The necrosis of the myocardial musculature and of the walls of the arterioles is non-inflammatory. Necrosis is in many cases obviously not vascular in origin since it is often not associated with changes in the coronary arteries; arteriolar changes are usually partly or completely circumferential and distributed in a segmental fashion.

It is possible by various manipulations on the kidney such as bilateral nephrectomy, ligature of the ureters and implantation of one ureter into the gut with removal of the contralateral kidney so to modify conditions as to have an elevation of blood pressure or maintenance of normal pressure levels. By use of artificial measures the level of the waste products in the blood can be maintained at any desired level. By such experiments it has been possible to correlate the pathologic findings with the blood pressure levels and the level of catabolites and to determine the probable relationship between these factors and their relation to the findings in malignant hypertension.

COMPARATIVE EFFECTS OF VERTAVIS, SODIUM DEPLETION AND SODIUM REPLETION IN ESSENTIAL HYPERTENSION. *A. Ruskin, M.D., A. J. Rider, M.D., (by invitation) B. Ruskin, M. S., J. A. Scott, M.D. and H. Rabinowitz, M.D. Galveston, Tex.* (From the University of Texas, Medical Branch.)

Thirty-one patients with uncomplicated essential hypertension were placed on five regimens of three weeks each of placebo, vertavis, marked sodium depletion and repletion, and vertavis plus sodium depletion. Depletion of sodium was accomplished by 200 mg. sodium chloride diet and mercuhydrin or thiomerin 2 cc. twice weekly. Sodium repletion consisted of the administration by mouth of 9 to 12 gm. each of sodium chloride and sodium bicarbonate in divided doses daily.

Statistical evaluation of all pressures during various regimens, contrasted with placebo periods, revealed: (1) significant hypotensive effects in most cases following vertavis administration in recommended ascending dosage, side effects frequent; (2) greater hypotensive effects, with fewer side effects, after sodium depletion; (3) elevation of blood pressure above the placebo level in several cases with sodium repletion and (4) greater hypotensive effects on the combined vertavis and sodium depletion regimen in some cases than from either alone.

Serum sodium levels often decreased significantly following marked sodium depletion with or without vertavis, and less so after veratrum

viride alone. Vital capacities were unaffected except for significant rises in two cases thrown into heart failure by sodium repletion. Etamon floors were not infrequently lowered by sodium depletion, and remained generally unchanged under other regimens.

OBSERVATIONS ON SMOOTH MUSCLE FOLLOWING SYMPATHECTOMY. *Homer D. Kirgis, M.D. and Adrian F. Reed, M.D. (by invitation) New Orleans, La.* (From the Department of Anatomy, Tulane University School of Medicine, Section on Neurosurgery, Ochsner Clinic, and Department of Anatomy, Tulane University School of Medicine.)

Observations have been made on the activity of the dilator pupillae and the retractor of the nictitating membrane of the cat following preganglionic, ganglionic and postganglionic types of sympathectomy. The activity of these muscles following these procedures has been compared with similarly sympathectomized animals which have also been subjected to a unilateral or bilateral adrenalectomy. Implants of adrenal cortex or of pellets of desoxycorticosterone were made into the animals which previously had the adrenal glands removed bilaterally. Some animals were subjected to a ganglionic sympathectomy on the right and preganglionic sympathectomy on the left. Evidence of functional regeneration of the severed axons has been observed after preganglionic and postganglionic sympathectomy. The muscles have remained relatively completely inactivated following ganglionic sympathectomy. Those animals which have had a preganglionic or postganglionic sympathectomy have demonstrated hyperactivity of the experimental muscles, usually after approximately five months have elapsed postoperatively. The phenomenon has persisted. Bilateral adrenalectomy did not prevent hyperactivity of the experimental muscles with the animal under general anesthesia after ganglionic or preganglionic sympathectomy.

OBSERVATIONS ON REVERSAL OF THE PRESSURE GRADIENT IN THE PULMONARY CIRCUIT. *John L. Cannon, M.D. (Introduced by James V. Warren, M.D.) Atlanta, Ga.* (From the Department of Physiology, Emory University School of Medicine.)

The dynamics of pulmonary circulation were studied in a series of anesthetized dogs before and during infusion of physiologic saline solution into the pulmonary artery and after administration of epinephrine. Pulmonary arterial and pulmonary venous pressures were recorded from intravascular catheters. Nearly simultaneous determinations of cardiac output and pulmonary blood volumes were carried out by the dye method.

Pulmonary venous pressure in the untreated anesthetized animals was found in most instances to rise slightly above pulmonary arterial pressure in late diastole. Following the saline infusion the venous pressure was higher than the arterial for a major part of diastole, with both pressures showing a gradual rise as the infusion progressed. Cardiac output was increased at this time but the pulmonary blood volume was increased slightly or not at all. Epinephrine produced an even greater prolongation and increase in the magnitude of this pressure gradient reversal which in several dogs was followed by pumlonary edema and death. Under these circumstances epinephrine produced a decrease in cardiac output and an increase in pulmonary blood volume.

MECHANISMS OF CHEYNE-STOKES RESPIRATION. *William W. Pryor, M.D. (Introduced by E. Charles Kunkle, M.D.) Durham, N.C.* (From the School of Medicine, Duke University.)

The mechanisms responsible for Cheyne-Stokes breathing have not been well explained. In the present study determinations have been made of the oxygen and carbon dioxide contents and the pH of multiple arterial blood samples drawn during various phases of the respiratory cycle in patients with Cheyne-Stokes respiration. Measurements of the arm to lung and arm to tongue circulation time have also been made.

Results indicate that in certain cardiac patients the development of Cheyne-Stokes breathing may depend upon the following three factors: (1) moderate decrease in the sensitivity of the respiratory center; (2) great prolongation in the mean time required for blood to pass from the pulmonary capillaries to the arterial tree; this results from the large volume of residual blood in the left heart; and (3) rapid fall in oxygen content of blood passing through a congested lung when respiration is slowed or stopped. This results in a considerable lag in response of the respiratory center to the degree of aeration of blood in the lung, and in a rapid development of anoxia in lung blood while

the chemoreceptors and respiratory center are bathed in well aerated blood.

In patients with uremia the situation is more complicated. Results suggest that delay in response of the respiratory center or a periodic change in sensitivity of the center may play a part in the development of Cheyne-Stokes breathing in this condition.

RESPONSE OF THE HUMAN CRANIAL VASCULAR TREE TO THE INVERTED POSITION. *E. Charles Kunkle, M.D., John B. Pfeiffer, M.D. and Courtland H. Davis, M.D. Durham, N.C.* (From the Department of Medicine (Neurology). Duke University School of Medicine.)

In the head-down position cranial arteries and veins are exposed to increased intravascular pressure. Cranial symptoms and signs under this physical stress have been analyzed in twenty-one adult human subjects on a tilt-table turned 50 to 60 degrees to the horizontal.

The head fullness and facial flushing initially noted after inversion commonly diminished in intensity within fifteen to sixty seconds. This observation was reinforced by interviews with circus performers accustomed to the effects of the head-down position. These witnesses reported, also, that the adaptation is enhanced by daily practice.

In studies of individuals with clinical or experimentally induced vascular headache such headache has been frequently observed to subside in part or entirely during head-down tilting although the responses were variable. Characteristics of the headaches investigated indicated that they were probably associated with dilatation of extracranial or intracranial arteries. The relief of headache in the inverted position was shown not to depend upon alterations in pain perception *per se*.

These preliminary observations do not clearly define the behavior of the various segments of the cranial vasculature when the head is dependent. It is relevant, however, that others have reported a rise in cerebrovascular resistance in the subject tilted 20 degrees head down. The available clinical and experimental evidence thus suggests that vasoconstriction may occur in branches of both internal and external carotid systems in adaptation to the inverted position. A final conclusion is not yet possible.

STUDY OF ANTIDIURETIC EFFECTS OF THE DEPRESSANT DRUGS USED IN ECLAMPSIA. *Willis E. Brown, M.D., Robert E. Hodges, M.D. (by invitation) and J. T. Bradbury, Sc.D., Little Rock, Ark.*

During the course of studies on sodium and water excretion of pregnant women, it was observed that morphine elicited an antidiuretic response. It seemed possible that the oliguria of toxemia might be converted to anuria by heavy morphine sedation. Several possible explanations for this antidiuretic effect were considered, namely, changes associated with sleep itself, a release of antidiuretic hormone from the pituitary (suggested by de Bode) or a direct action on the kidney. Experiments were established to study this effect and to learn its application to toxemia and eclampsia.

Under controlled experimental conditions the effects of morphine and other depressants on the urine volume were studied. Hypnotism, which was used to check the effect of sleep *per se*, failed to alter urine volume. A study of many of the commonly used drugs suggested that some were diuretic and others antidiuretic.

Studies of cases of diabetes insipidus suggested that the pituitary is not necessary for the antidiuretic effect of morphine.

Intrarenal changes were studied by the use of thiosulfate and hippurate clearances. These experiments suggest that the morphine antidiuresis is accomplished by the dual mechanism of reduced plasma flow and increased tubular reabsorption.

Adrenalin and pitressin were studied as examples of hormonal control of urine volume. These observations suggest that pitressin antidiuresis is accomplished primarily by an increased tubular reabsorption while adrenalin antidiuresis is primarily through a decrease in plasma flow.

Avertin and amytal appear to lack the antidiuretic effect of morphine and other narcotics, and might be preferable drugs to control the convulsions of eclampsia.

ARTIFICIAL PNEUMOPERITONEUM IN THE TREATMENT OF PULMONARY EMPHYSEMA: PRELIMINARY REPORT. *James J. Callaway, M.D. (by invitation) and Robert H. Furman, M.D. Nashville, Tenn.* (From the Departments of Medicine and Physiology, Vanderbilt University School of Medicine.)

The treatment of pulmonary emphysema with artificial pneumoperitoneum was introduced by Reich in 1924, and subsequent reports of Piaggo

Blanco and his associates in 1937 indicated that this therapy provided definite benefit in a significant number of cases. Nevertheless, artificial pneumoperitoneum has not been widely used in the treatment of pulmonary emphysema. This report reviews briefly the abnormal pneumodynamics of pulmonary emphysema, considers the physiologic basis for this form of treatment and presents a preliminary report of the results obtained with this treatment in seven severe cases.

Pretreatment studies include chest x-rays in maximal inspiratory and expiratory positions, vital capacity studies, electrocardiograms and exercise tolerance utilizing the Millikan Oximeter and the Master two-step. After pneumoperitoneum treatment, vital capacity studies, exercise tolerance and chest x-rays were again obtained. In each instance there was an increase in vital capacity and an increase in exercise to erance following pneumoperitoneum. There was moderate to marked subjective improvement and frequent diminution in associated asthmatic attacks. There were no significant changes evident in the electrocardiogram following treatment which could be directly attributed to the pneumoperitoneum other than for some change in the electrical axis.

# Case Reports

## Evidence against Renal Vascular Shunts in a Case of Lower Nephron Nephrosis*

JOHN K. CLARK, M.D., HAROLD G. BARKER, M.D. *and* ARCHER P. CROSLEY, JR., M.D.
*Philadelphia, Pennsylvania*

IT has been recently suggested by Trueta et al.[1] that anuria in crushing injuries, sulfonamide toxicity, incompatible blood transfusions, black water fever and many other conditions resulting in "lower nephron nephrosis"[2] may be due to reflex stimulation of intrarenal vascular shunts whereby blood is diverted away from the cortex through specialized juxtamedullary glomeruli and medullary vasa recta to the renal vein. This should result in arterialization of renal venous blood with respect to all constituents. We have therefore analyzed renal venous and arterial blood from a patient anuric as a result of an incompatible blood transfusion in order to test this hypothesis.

### CASE REPORT

A twenty-nine year old Rh-negative white female was admitted to the University Hospital July 19, 1949, having been anuric or oliguric for eight days following reaction to a transfusion given elsewhere on July 11, 1949. She had been given Rh-positive blood in the course of treatment for a complete septic abortion in the third month of her seventh pregnancy. Her husband was Rh-positive and the patient showed a strong anti-Rh titer. She had also been given 1 gm. of a mixture of sulfadiazine, sulfamerazine and sulfathiazole on July 11th. On admission she was mentally clear and cooperative, her chief complaint being persistent nausea and vomiting.

Physical examination revealed the following: temperature 98.6°F., pulse 68 per minute, respiration 24 per minute, blood pressure 125/75 mm. Hg. She showed moderate generalized edema, foul vaginal discharge and slight costovertebral tenderness. Otherwise physical findings were not abnormal. Laboratory studies: Hemoglobin 10.1 gm. per 100 ml., white blood count 16,000/cu. mm., blood urea nitrogen 91 mg. per 100 ml., creatinine 16.4 mg. per 100 ml., uric acid 15.9 mg. per 100 ml., calcium 7.3 mg. per 100 ml., phosphorus 11 mg. per 100 ml., total bilirubin 0.77 mg. per 100 ml., chlorides 80 mEq./L., sodium 125 mEq./L., potassium 4.8 mEq./L., carbon dioxide content 19.8 mEq./L. (45 volumes per cent).

Her urinary output was 60 cc. on the day of admission and did not exceed 100 cc. for the next three days. She was treated conservatively with intravenous fluids and electrolytes in amounts calculated to replace loss and restore deficiencies (2,200 cc. of water, 200 gm. of glucose and 300 mEq. of sodium chloride daily during the period of oliguria). She gradually developed a spontaneous diuresis, her urinary output being 300 cc. on July 23rd and 1,740 cc. on July 27th.

She was discharged on August 7th clinically asymptomatic although somewhat anemic (Hb 43 per cent) and slightly azotemic (BUN 35). Her urine showed traces of albumin but it was believed she had probably suffered no permanent renal damage.

### METHODS

These studies were carried out on the nineth day of oliguria (July 20, 1949). The output for the twenty-four-hour period ending that morning was 60 cc.

Simultaneous blood samples were taken from the right renal vein (catheter) and femoral artery twenty-five minutes before,

* From the University of Pennsylvania School of Medicine and Hospital, Philadelphia, Pa. This work was supported by the Department of Medicine, the Harrison Department of Surgical Research, the William Pepper Laboratory, and the C. Mahlon Kline Fund for developments in the Department of Medicine.

and forty-six and seventy-five minutes after the intravenous injection of 600 mg. of p-amino-hippurate (PAH) and 12.5 gm. of mannitol. The bladder was washed by means of a catheter before injection of PAH and mannitol and at the end of the test, although only a few drops of urine were being formed.

Serum sodium and potassium were determined by means of a flame photometer on specimens taken into dry syringes and immediately transferred under oil for centrifugation. Chloride was determined on these specimens by Eisenman's method.[3]

Determinations of plasma creatinine,[4] mannitol,[5] free PAH[6] and total PAH[7] by the methods indicated were made on blood taken into dry syringes and transferred to tubes containing powdered heparin. Aliquots of this blood placed in oxalate tubes were analyzed for urea nitrogen by direct Nesslerization of barium hydroxide, zinc sulfate filtrates in the presence of gum ghatti following treatment of whole blood with urease prepared according to Koch's method.[8]

Samples for gas analysis were taken anaerobically into heparinized 10 cc. syringes, 1 cc. of mercury was introduced, the syringes were immediately capped and stored in ice until analyzed, less than two hours after being drawn during which time no measurable change occurs. Oxygen and carbon dioxide content were determined in duplicate on 1 ml. blood samples by the manometric method of van Slyke and Neill for simultaneous determination.[9]

Oxyhemoglobin concentration was determined in triplicate by means of an Evelyn colorimeter. The values reported were determined on blood from the tubes containing powdered heparin. This measures changes in concentration due to passage through the kidney or dilution by saline remaining in the venous catheter. Oxyhemoglobin determinations were also made on the blood samples taken for gas analysis in which the additional possibility of unequal dilution of arterial and venous blood by the liquid heparin exists. Since in this case correction of the determined blood gas values for the slight arteriovenous differences in hemoglobin concentration would change the mean renal A-V oxygen difference by only 0.05 volume per cent, the uncorrected figures are reported.

Hematocrits were determined in duplicate according to Wintrobe,[10] no correction being made for trapped plasma.

Blood pH was determined by means of a glass electrode on a Cambridge meter at room temperature and this value corrected to 37°c.[11]

## RESULTS

The data are given in Table 1. They show a greatly reduced extraction of mannitol, creatinine, urea and PAH (substances excreted rapidly by the normal kidney with extractions of roughly 20, 20, 10 and 90 per cent respectively), with an entirely normal arteriovenous difference for oxygen and carbon dioxide. Accompanying the very small extractions of the excretory substances, minute amounts of mannitol, creatinine and PAH, inadequate for clearance calculations, were recovered in the bladder washings. Extraction of chloride, sodium, potassium and water (hemoglobin and hematocrit) was essentially zero. The pH of the renal venous blood did not differ by a measurable amount from that of the arterial samples.

## COMMENTS

The small or immeasurable A-V difference of pH, oxyhemoglobin and hematocrit does not differ from the normal kidney where, as in this patient, the extraction of chloride, sodium and potassium should also be undetectable. These results merely indicate that no measurable dilution, concentration or contamination of the specimens occurred.

The combination of extremely small extractions of creatinine, urea, mannitol and PAH with normal renal A-V differences of oxygen and carbon dioxide excludes arteriovenous shunting alone as the mechanism of anuria; since if this were the case, arterialization should be demonstrated to an equal

degree for all constituents. It can also be stated that blood is not perfusing a small amount of normal tissue exclusively since under these circumstances the extractions of the excretory substances would not be reduced. To be compatible with the data, any theory of intrarenal hemodynamic short-circuiting would have to postulate either perfusion of almost entirely non-excretory tissue, which is unlikely in view of the patient's eventual recovery, or the association of (1) perfusion of the bulk of renal tissue within a reduced amount of blood, from each volume of which an increased amount of oxygen was removed, and (2) shunting and arterialization of the major fraction of the blood thus reducing the excretory extractions by dilution and resulting in a normal over-all oxygen and carbon dioxide A-V difference. On the hemodynamic level this hypothesis requires simultaneous vasoconstriction and vasodilatation in the renal vascular bed; on the metabolic level it requires increased removal of oxygen from each volume of perfusing blood with the coincidence that the net result on A-V difference remains just normal.

TABLE I

COMPARISON OF VARIOUS SUBSTANCES IN SIMULTANEOUS SAMPLES OF ARTERIAL AND RENAL VENOUS BLOOD

| Substance | Unit | Blood Sample | | | | | | Mean | |
|---|---|---|---|---|---|---|---|---|---|
| | | 1 | | 2 | | 3 | | | |
| | | A* | R* | A | R | A | R | A-R | Amt. Extracted %* |
| Creatinine | mg./100 ml. | 16.4† | 15.7† | ..... | ..... | ..... | ..... | 0.7 | 4.3 |
| Mannitol | mg./100 ml. | ..... | ..... | 60.7 | 59.7 | 58.2 | 53.3 | 3.0 | 5.0 |
| Urea nitrogen | mg./100 ml. | 99 | 94 | ..... | ..... | ..... | ..... | 5.0 | 5.1 |
| Free PAH | mg./100 ml. | ..... | ..... | 3.15 | 3.10 | 2.80 | 2.75 | 0.05 | 1.7 |
| Total PAH | mg./100 ml. | ..... | ..... | 3.60 | 3.25 | 3.38 | 3.17 | 0.28 | 8.0 |
| Chloride | mEq./L. | 74 | 74 | ..... | ..... | ..... | ..... | 0 | 0 |
| Sodium | mEq./L. | 127 | 127 | ..... | ..... | ..... | ..... | 0 | 0 |
| Potassium | mEq./L. | 4.5 | 4.5 | ..... | ..... | ..... | ..... | 0 | 0 |
| Hemoglobin | gm./100 ml. | 9.10 | 9.17 | 9.02 | 9.02 | 8.88 | 8.88 | 0.02 | .... |
| Hematocrit | ..... | .315 | .320 | .300 | .305 | .295 | .300 | −0.005 | .... |
| pH | ..... | 7.36 | 7.31 | 7.30 | 7.31 | 7.36 | 7.31 | 0.02 | .... |
| Oxygen | Vol. % | 11.86 | 10.47 | 11.63 | 10.03 | 11.41 | 9.82 | 1.53 | 13.1 |
| $CO_2$ | Vol. % | 31.3 | 32.6 | 30.7 | 32.0 | 30.6 | 31.3 | −1.1 | .... |

* A = Arterial (systemic) concentration; R = renal venous concentration; Amt. Extracted % = (A-R) 100/A.
† Serum from the three samples was pooled.

In the normal kidney when blood flow is reduced by hemorrhagic shock in the dog[12] or by abdominal compression in man[13] the A-V oxygen difference remains essentially constant with a resulting reduced total renal oxygen consumption parallel to the flow changes. The renal A-V oxygen difference may increase, however, in man

during the reduced renal blood flow of congestive failure[14] or tilting,[15] and in the dog with extreme reductions of hemorrhagic shock.[12] Since at present no clinical method for measuring renal blood flow during anuria exists, it is impossible to calculate the total renal oxygen consumption. Moreover, the metabolic pattern of the kidney in lower nephron nephrosis may be different from the normal and, since even in the normal kidney the pattern may change with the experimental conditions, the A-V oxygen difference itself gives no indication as to total blood flow or oxygen consumption.

Our data are entirely consistent with perfusion of the entire kidney by an unknown amount of blood, the anuria and reduced excretory extractions being due to unselective reabsorption of glomerular filtrate by damaged tubular epithelium as demonstrated by direct microscopic observation by Richards[16] in the living amphibian kidney, the normal A-V oxygen and carbon dioxide differences being due to the ordinary requirements of living cells. This interpretation is further supported by the finding of a negative Tm PAH preceding the progressive restoration of normal functional pattern during recovery in a similar case due to sulfathiazole poisoning reported by Redish et al.[17] The data are also entirely compatible with the assumption of precipitation of heme compounds in the tubules with resultant obstructive anuria.

## SUMMARY

1. In an anuric patient renal extraction of creatinine, mannitol, urea and PAH was found to be extremely low and that of water, chloride, sodium and potassium essentially zero.

2. The renal A-V oxygen and $CO_2$ differences were entirely normal.

3. The hypothesis of renal vascular shunts alone seems untenable under these conditions.

4. The properties of a shunting mechanism necessary to explain the data are defined.

5. The data do not exclude unselective reabsorption of glomerular filtrate or mechanical obstruction of renal tubules as the mechanism of anuria.

## REFERENCES

1. Trueta, J., Barclay, A. E., Daniel, P. M., Franklin, K. J. and Prichard, M. M. L. Studies of the Renal Circulation. Springfield, Ill. 1947. Charles C Thomas.
2. Lucké, B. Lower nephron nephrosis. *Mil. Surgeon*, 99: 371, 1946.
3. Eisenman, A. A note on the van Slyke method for the determination of chloride in blood and tissue. *J. Biol. Chem.*, 82: 411, 1929.
4. Brod, J. and Sirota, J. H. The renal clearance of endogenous "creatinine" in man. *J. Clin. Investigation*, 27: 645, 1948.
5. Barker, H. G. and Clark, J. K., Effect of p-aminohippurate on mannitol determinations by the periodate-iodide-thiosulfate method. *Proc. Soc. Exper. Biol. & Med.*, 64: 120, 1947.
6. Smith, H. W., Finkelstein, N., Aliminosa, L., Crawford, B. and Graber, M. The renal clearances of substituted hippuric acid derivatives and other aromatic acids in dog and man. *J. Clin. Investigation*, 24: 388, 1945.
7. Newman, E., Kattus, A., Genecin, A., Genest, J., Calkins, E. and Murphy, J. Observations on the clearance method of determining renal plasma flow with diodrast, para-aminohippuric acid (PAH) and para-acetylaminohippuric acid (PACA). *Bull. Johns Hopkins Hosp.*, 84: 135, 1949.
8. Koch, F. C. A stable and convenient urease reagent and a modified blood urea method. *J. Lab. & Clin. Med.*, 11: 776, 1926.
9. van Slyke, D. D. and Neill, J. M. The determination of gases in blood and other solutions by vacuum extraction and manometric measurement. *J. Biol. Chem.*, 61: 523, 1924.
10. Wintrobe, M. M. A simple and accurate hematocrit. *J. Lab. & Clin. Med.*, 15: 287, 1929.
11. Rosenthal, T. B. The effect of temperature on the pH of blood and plasma in vitro. *J. Biol. Chem.*, 173: 25, 1948.
12. Dale, V. P., Emerson, K., Jr., Phillips, R. A., Hamilton, P. and van Slyke, D. D. The renal extraction of oxygen in experimental shock. *Am. J. Physiol.*, 145: 337, 1946.
13. Bradley, S. E. and Halperin, J. H. Renal oxygen consumption in man during abdominal compression. *J. Clin. Investigation*, 27: 635, 1948.
14. Mokotoff, R., Escher, D. J. W., Edelman, I. S., Grossman, J., Leiter, L., Weston, R. E., Zweifach, B. W. and Shorr, E. Studies on vasotropic principles in blood (VEM and VDM) and renal hemodynamics in chronic heart failure. *Federation Proc.*, 8: 112, 1949.
15. Clark, J. K., Barker, H. G. and Crosley, A. P., Jr. Unpublished data.
16. Richards, A. N. Direct observations of change in function of the renal tubule caused by certain poisons. *Tr. A. Am. Physicians*, 44: 64, 1929.
17. Redish, J., West, J. R., Whitehead, B. W. and Chasis, H. Abnormal renal tubular back-diffusion following anuria. *J. Clin. Investigation*, 26: 1043, 1947.

# Para-aminobenzoic Acid in the Treatment of Acute Rheumatic Fever*

ROBERT J. HOAGLAND, M.D.
*West Point, New York*

ALTHOUGH specificity of action of salicylates in rheumatic fever is still a controversial question, evidence has accumulated indicating the probability of specific effects. Hyaluronidase has been incriminated in the pathogenesis of rheumatic fever and salicylates have been shown to have an inhibitory effect on hyaluronidase both *in vivo* and *in vitro*.[1,2] Furthermore, it is possible that salicylates may affect the course of rheumatic fever by inhibiting antibody formation. At any rate, for some years a high salicylate level has been advocated by Coburn[3] and other investigators for the most effective treatment of rheumatic fever.

Para-aminobenzoic acid (paba) is considered to be part of the vitamin B complex. It is also believed to form part of the structure of the folic acid complex.[4] Hamilton[5] believes that paba has a blocking action on an enzyme system of rickettsiae. Possibly, a similar action of paba on enzyme systems in the human body might alter the course of acute rheumatic fever. In any event, Dry, Butt and Scheifley[6] showed that salicylate blood levels were increased by the concomitant administration of paba, and solely by such action paba might benefit patients with rheumatic fever receiving salicylates. Salassa et al.[7] confirmed the work of Dry and stated that the oral administration of paba altered the detoxification of salicylate by affecting the conjugation of glycine with salicylate so that only very small amounts of salicyluric acid appeared in the urine. Paba also lowered the pH of the urine which decreased the renal clearance of free salicylate. Parker[8] stated that paba decreased excretion of free salicylate in the urine but alkalinization of urine was accompanied by increased excretion of free salicylate.

Dry, Butt and Scheifley reported a case of a man with typical acute rheumatic fever who did not show a response to a liberal intake of salicylate (10 gm. daily with an equal amount of sodium bicarbonate) but who responded dramatically when paba was administered simultaneously (2 gm. every two hours). They observed a steady increase of salicylate blood levels and complete clinical response when the blood level reached 37.5 mg. per 100 cc. of blood. Rosenblum and Fraser[9] used paba alone in nine cases of rheumatic fever and reported a favorable effect on fever and joint pains. It is hard to concur in their reasoning that a favorable effect of paba might be expected because patients with rheumatic fever and rickettsial diseases both have vasculitis; and since paba is effective in the latter group of diseases, it might be beneficial in the former. Without disputing the favorable effects reported, one might conclude that they had nothing to do with vasculitis. Possibly the effect of paba on enzyme systems may be a factor in any favorable effect.

Inasmuch as the patient whose case was reported by Dry and associates responded so dramatically when paba was added to his salicylates, their lead was followed in treating a patient who was receiving gr. 150 of aspirin daily without the desired results. Since unsatisfactory response to salicylate therapy is unusual in rheumatic fever and since there have been so few reports of the

* From the Station Hospital, West Point, N. Y.

augmentation of salicylate effect by paba, this case appears worth reporting.

CASE REPORT

The patient, a twenty-three year old man, had no family history of rheumatic fever and no past history of rheumatic fever or of any of the rheumatic equivalents. He had scarlet fever in childhood and an appendectomy in 1945.

In January, 1948, one month before admission to the hospital, he noticed malaise and a mild aching in the area of his right shoulder joint which persisted until entry into the hospital. Discomfort in the right ankle and in the base of the right great toe were experienced about a week later. Then the left big toe and ankle, left shoulder and right knee became painful in rapid succession. The right knee was slightly swollen for a day but no other joint redness or local heat was noted. Afternoon elevations of temperature were suspected by the patient but he did not take his temperature. About two weeks before admission he experienced a non-productive cough which lasted about four days.

Physical examination on admission in February revealed no significant abnormalities except a soft, grade I, brief systolic murmur at the apex, and a slight swelling and increased temperature of the right knee. Raising the right arm produced mild pain in the right deltoid area.

Sedimentation rate on admission was very rapid (38.5 mm. in one hour—Wintrobe method), electrocardiogram was normal and the antistreptolysin titer was between 250 and 300 units/cc. Hematologic examination gave normal results. Skin tests for brucellosis and trichinosis were negative.

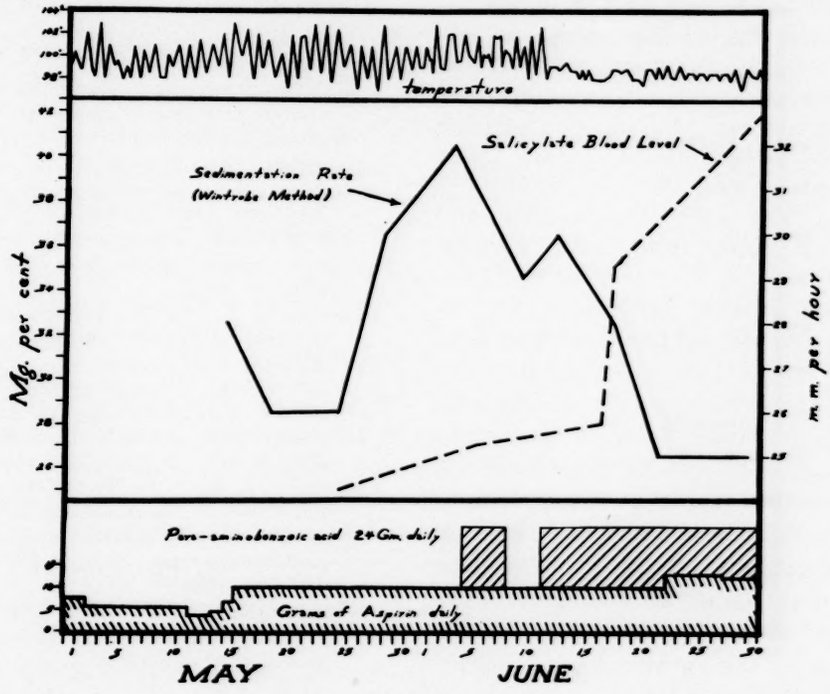



FIG. 1.

The temperature reached peaks of 101°F. for a week after admission, when daily administration of 5 gm. of aspirin was begun with coincident disappearance of fever. Except for one rise to 103.8°F. his temperature remained normal for about two months, but the sedimentation rate remained between 18 and 30 mm./hour and an increase of P-R interval to .25 second was detected in electrocardiograms. Despite continuous use of aspirin, joint aching and fever recurred with daily temperature peaks of 101° to 103°F. The sedimentation rate remained accelerated (26 to 30 mm.). For about five weeks symptoms continued unaffected by treatment. Numerous blood cultures were sterile. Agglutination tests for undulant fever, typhoid and paratyphoid, which were all negative during the first week of hospitalization, were still negative. A moderately severe normocytic anemia appeared.

On June 5th, 2 gm. of paba were given every two hours around the clock. The supply of the drug lasted only four days and the same dose was

resumed on June 12th on which day his temperature became and remained normal. His weight, which had decreased from an initial 165 to 150 pounds, simultaneously began an uninterrupted ascent and he felt and remained free of all symptoms.

The salicylate level, which was 25 mg. per 100 cc. of blood before the start of paba, increased to 42 mg. during the course of this treatment. On July 8th, after thirty days of paba, his leukocyte count dropped to 2,300 with 41 per cent neutrophiles. Since he had been afebrile and symptomless for twenty-seven days, paba was discontinued without affecting his feeling of good health. The sedimentation rate and electrocardiogram slowly returned to normal. (Fig. 1.)

Follow-up examination in July, 1949, revealed continuation of good health and no signs of disease.

## COMMENT

High blood level of salicylates is believed to produce optimum results in the treatment of acute rheumatic fever. The blood level of salicylates is increased by the simultaneous administration of paba In addition, paba itself may have a beneficial action on the disease process of rheumatic fever Therefore, when response to salicylates is unsatisfactory, a patient with rheumatic fever should receive paba in addition. Beneficial effect should be manifested by the disappearance of symptoms and fever.

## SUMMARY

A case of rheumatic fever with refractoriness to 10 gm. of aspirin daily manifested by an uninterrupted fever for five weeks showed dramatic improvement after the addition of para-aminobenzoic acid in a dose of 24 gm. daily.

## REFERENCES

1. Guerra, Francisco. Hyaluronidase inhibition by sodium salicylate in rheumatic fever. *Science*, 103: 686–687, 1946.
2. Dorfman, A., Reimers, E. J. and Ott, M. L. Action of sodium salicylate on hyaluronidase. *Proc. Soc. Exper. Biol. & Med.*, 64: 357–360, 1947.
3. Coburn, A. F. Salicylate therapy in rheumatic fever; a rational technique. *Bull. Johns Hopkins Hosp.*, 73: 435–464, 1943.
4. Gale, E. F. Nitrogen metabolism of gram-positive bacteria. *Bull. Johns Hopkins Hosp.*, 83: 119–175, 1948.
5. Hamilton, H. Effect of para-aminobenzoic acid on growth of rickettsiae and elementary bodies, with observations on mode of action. *Proc. Soc. Exper. Biol. & Med.*, 59: 220–226, 1945.
6. Dry, T. J., Butt, H. R. and Scheifley, C. H. The effect of oral administration of para-aminobenzoic acid on the concentration of salicylates in the blood: preliminary report. *Proc. Staff Meet., Mayo Clin.*, 21: 497–504, 1946.
7. Salassa, R. M., Bollman, J. L. and Dry, T. J. Effect of para-aminobenzoic acid on metabolism and excretion of salicylate. *J. Lab. & Clin. Med.*, 33: 1393, 1948.
8. Parker, W. A. Factors influencing plasma concentration of salicylate. *Quart. J. Med.*, 17: 229, 1948.
9. Rosenblum, H. and Fraser, L. E. Effect of para-aminobenzoic acid on fever and joint pains of acute rheumatic fever. *Proc. Soc. Exper. Biol. & Med.*, 65: 178–182, 1947.

# Book Reviews

**The Epitome of Andreas Vesalius.** Translated by L. R. Lind, with anatomical notes by C. W. Asling. New York, 1949. The Macmillan Co. *Price* $7.50.

The *Epitome*, prepared by Vesalius in 1543 and in effect a condensed version of the *Fabrica*, is now made available for the first time in English translation. To each of the chapters is appended a general interpretation and also detailed explanatory notes so that the text, which despite all difficulties is clearly rendered in modern phraseology, is readily followed. The original Latin translation is also given and here, too, are the famous wood-cuts, somewhat the worse for reduction in reproduction.

The *Epitome*, of course, is one of the great anatomic works of all time. But, as Dr. Lind points out, Vesalius has been more often praised than read. Here is the opportunity to read and own the text which, together with the *Fabrica*, laid the foundation of modern anatomy.

A. B. G.

**Evaluation of Chemotherapeutic Agents.** Colin M. MacLeod, M.D., Editor. 205 pages. New York, 1949. Columbia University Press. *Price* $4.00.

This is the second in a series of Symposia to be published by the Section on Microbiology of the New York Academy of Medicine. The material herein presented critically evaluates certain of the factors responsible for the clinical effectiveness of various chemotherapeutic and antibiotic agents. As stated by the Editor in the Symposium's introduction, the discussions are broad in their scope with no attempt being made to consider specific therapy of individual diseases.

The well chosen subject matter, carefully prepared by authorities in the field, provides a volume of interest and importance to those concerned with the treatment of infectious diseases. The arrangement of the various chapters is logical in its sequence, with the first portion of the book covering certain broad subjects. These include plasma and blood concentrations, the relationship between these levels and chemotherapeutic activity, the binding of various agents to proteins, microbial resistance, defense mechanisms of the host and the nature and location of the lesion as an influence both on host defense and drug activity.

The more particular problems concerned with local therapy of soft tissue infections, with meningococcal infections and bacillary dysentery, with streptococcal chemoprophylaxis, with the use of antimalarial drugs, and with rickettsial and viral infections are subsequently presented. The final chapters of the Symposium, which consider the chemotherapeutic approach to neoplastic diseases, are well done, but mark a definite departure from the general subject matter.

A. R. L., Jr.

**Diseases of the Aorta. Diagnosis and Treatment.** Nathaniel E. Reich, M.D. F.A.C.P. New York, 1949. Macmillan Co. *Price* $7.50.

Dr. Reich has integrated into one volume knowledge concerning diseases of an organ which in the past have been a favorite challenge to the physical diagnostician and a particular delight to the pathologist. However, recent advances justify review of these former curiosities, many of which are now amenable to specific therapy. The author has wisely emphasized those conditions which can be treated.

The introductory chapter presents a concise general consideration of the normal anatomic, embryologic and physiologic mechanisms. The diseases are related according to gross etiologic or morphologic classification, and the greatest consideration is given to diagnosis while the broad principles of therapy are discussed. The final chapters are devoted to applicable diagnostic procedures and therapeutic tools.

The book is written in a pleasing, easily readable, well organized form. The illustra-

tions are excellent. On the whole, it is a useful and informative volume for the clinician.

M. C.

**Disease of the Heart.** Charles K. Friedberg, M.D. 1081 pages. Philadelphia, 1949. W. B. Saunders Co. *Price* $11.50.

The author has written a complete volume which includes the physiology, pathology, etiology, clinical features and treatment of various cardiac disorders. His direct emphasis is on our knowledge of how the process of disease arises and how it develops. He includes historical as well as present day concepts and indicates the many problems which remain unsolved.

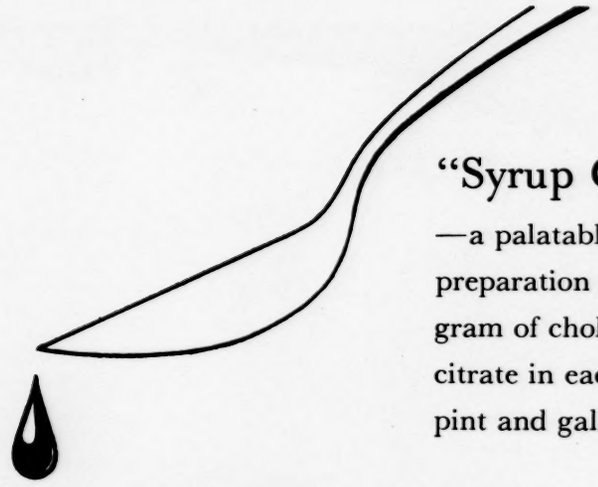
The section on coronary artery disease with all its manifestations is noteworthy for its clear presentation of a problem so often confused by other authors because of conflicting terminology. Cardiac failure and the theories put forth to explain its pathologic physiology are well covered. He includes excellent chapters on subjects usually omitted or passed over briefly in other works, namely, the heart in renal disease, pregnancy, the surgical patient, insurance and medicolegal problems, anemia, trauma and cardiac tumors.

The bibliography is complete. It is remarkably up-to-date, with references to works appearing in the literature within six months of the publication date of this book.

There are minor faults which are bound to present themselves in the first edition of a new work of such magnitude. The sections on electrocardiograms are brief with but few illustrations. It might be wiser to omit these sections entirely. This field has grown so large in scope that it would require a separate volume of equal size in order to be covered adequately. In classification there is a tendency to repetition and continual reference to some other section or chapter which means that a reader must search through many pages to assemble the complete knowledge on any one desired subject.

It is to be hoped that Dr. Friedberg will continue to keep abreast of the advances in cardiology and will incorporate them into later editions of this book for it should prove to be a valuable addition to medical literature now available on cardiology for both medical student and internist.

J. A. L. M.



## "Syrup Choline (*Flint*)"

—a palatable and stable preparation containing one gram of choline dihydrogen citrate in each 4 cc. Supplied in pint and gallon bottles.

# SYRUP Choline

## CAPSULES

## "Capsules Choline (*Flint*)"

—containing 0.5 gram of choline dihydrogen citrate per capsule. Supplied in bottles of 100, 500 and 1000.

"Choline (Flint)" is indicated in the treatment of chronic liver involvement in diabetes, in malnutrition, in poisoning by hepatoxic agents, in various infectious processes and in cirrhosis.

*For your copy of "The Present Status of Choline Therapy in Liver Dysfunction"—write*

ACCEPTED COUNCIL ON PHARMACY AND CHEMISTRY AMERICAN MEDICAL ASSOCIATION

**FLINT, EATON & COMPANY**
DECATUR, ILLINOIS

| | Calories | Protein Gm. | Calcium Gm. | Copper mg. | Iron mg. | Phosphorus Gm. | Vitamin A I. U. | Thiamine mg. | Riboflavin mg. | Niacin mg. | Ascorbic Acid mg. | Vitamin D I. U. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| National Research Council Allowances, Sedentary Man (154 lbs.) | 2,400 | 70 | 1.0 | 1.2 | 12 | 1.5 | 5,000 | 1.2 | 1.8 | 12 | 75 | Small Amount |
| Ovaltine in Milk, 3 Servings * | 676 | 32 | 1.12 | 0.5 | 12 | 0.94 | 3,000 | 1.16 | 2.0 | 6.8 | 30 | 417 |
| Percentages of N. R. C. Allowances Provided by 3 Servings* of Ovaltine in Milk | 28% | 46% | 112% | 42% | 100% | 63% | 60% | 97% | 111% | 57% | 40% | Abundance |

*Each serving made of ½ oz. of Ovaltine and 8 fl. oz. of whole milk.

# Supplementation

## A sure step to dietary adequacy

The aim of the dietary at all times and under all conditions is to provide ample amounts—not just minimum amounts—of all nutrient essentials. Only when the daily nutrient intake is fully adequate, based on the most authoritative nutritional criteria, can the possibility of adequate nutrition be assured. It is for this reason that a food supplement assumes great importance in daily practice. It should be rich in those nutrients most likely deficient in prevailing diets or in restricted diets during illness and convalescence.

The *multiple nutrient dietary food supplement*, Ovaltine in milk, is especially suited for transforming even poor diets to full nutritional adequacy. This is clearly shown by the data in the table above.

Note in particular the high percentages of the dietary allowances for nutrients and the relatively low percentage of the total calories furnished by the servings of Ovaltine in milk. Thus, without unduly increasing the caloric intake, Ovaltine in milk greatly increases the contribution of nutrient essentials. Enticing flavor and easy digestibility are other important features of this dietary supplement.


Two kinds, Plain and Sweet Chocolate Flavored. Serving for serving, they are virtually identical in nutritional content.

Ovaltine

THE WANDER COMPANY, 360 N. MICHIGAN AVE., CHICAGO 1, ILL.

# appetite must be controlled

"The greatest problem in preventive medicine in the United States today is obesity."[1] And today it is well-known that *"The only way to counteract obesity . . . is by a restriction of food intake."*[2]

'Dexedrine' Sulfate controls appetite, making it easy for the patient to avoid overeating and thus to lose weight safely without the use (and risk) of such potentially dangerous drugs as thyroid. In weight reduction 'Dexedrine' *"is the drug of choice because of its effectiveness and the low incidence of undesirable side effects."*[1]
Smith, Kline & French Laboratories • Philadelphia

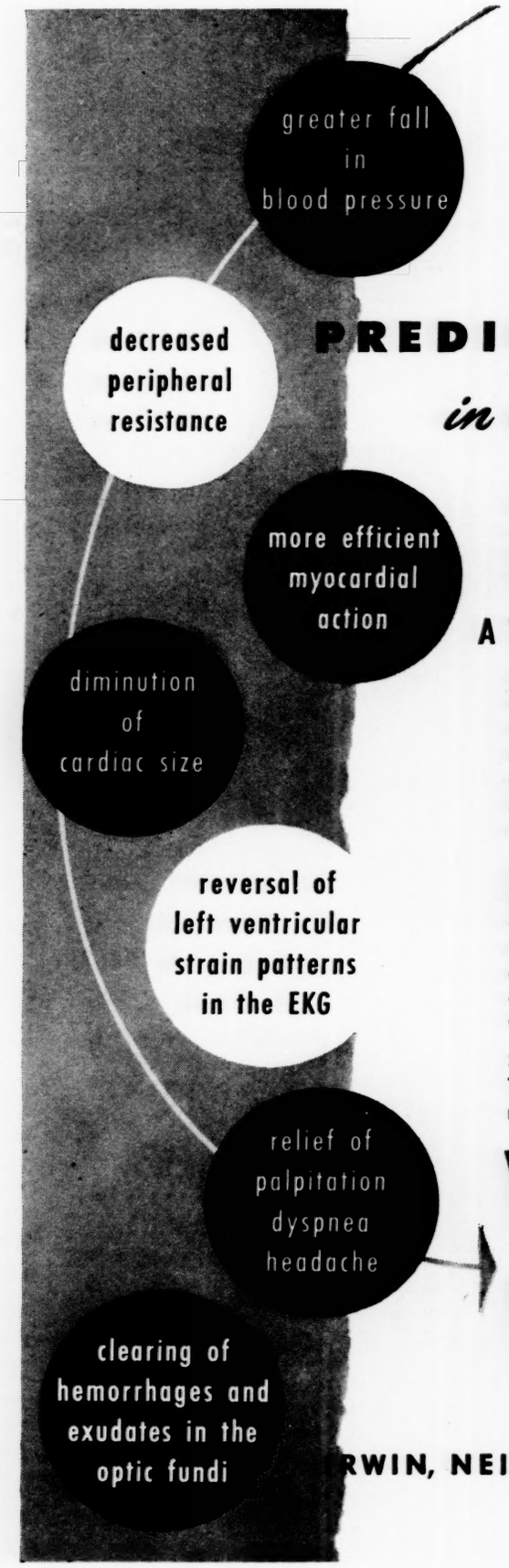
# Dexedrine* Sulfate tablets • elixir

**The most effective drug for control of appetite in weight reduction**

*T.M. Reg. U.S. Pat. Off.

1. Walker, W.J.: Obesity as a Problem in Preventive Medicine, U.S. Armed Forces M.J. 1:393, 1950.

2. John, H.J.: Dietary Invalidism, Ann. Int. Med. 32:595, 1950.




# PREDICTING RESPONSE

## *in essential hypertension*

Striking objective improvement, in the individual case, can be obtained with veratrum viride Biologically Standardized in Craw Units, as available in VERATRITE and VERTAVIS.

### A Therapeutic Alternative

*In mild and moderate hypertension* (Grades I and II), which accounts for more than 70 per cent of all hypertensive cases, VERATRITE is the choice of therapy and may be used routinely in everyday practice without undesirable side-effects. VERATRITE contains, in each tabule, veratrum viride (3 Craw Units) with sodium nitrite and phenobarbital.

*In severe, resistant hypertension* (Grade III) *and hypertension complicated by cardiac failure,* VERTAVIS can effect dramatic response. Adequate supervision of the patient and fine adjustment of dosage to the individual case are essential. VERTAVIS is a single agent, containing in each tablet veratrum viride (10 Craw Units).

Samples and literature on both VERATRITE and VERTAVIS, including clinical reports, are available on request.

**Veratrite®**
for mild and moderate hypertension

**Vertavis®**
for severe, resistant hypertension

**IRWIN, NEISLER & CO. • DECATUR, ILLINOIS**

# here's health . .

## to your patients . . . YEAR-'ROUND!

With Florida Frozen Concentrated Orange Juice—made from choice, fresh Florida oranges—the generous *daily* ingestion of refreshing, taste-tempting citrus juices is now a practical reality . . . and no trouble at all. The Frozen Concentrate preserves the delicious flavor of famed Florida oranges at their best—and comes to the consumer with the same high nutritional content as fresh juice. It is an excellent source of natural fruit sugars for easy-to-use energy,[2,3] and, by virtue of its notably high content of vitamin C with other nutrients,* assists markedly in improving stamina,[5] growth,[4] and resistance to disease.[1] Young and old, healthy and convalescent—virtually everyone benefits from consuming liberal amounts of citrus fruits and juices daily—whether frozen, fresh or canned.

**FLORIDA CITRUS COMMISSION**
**LAKELAND, FLORIDA**

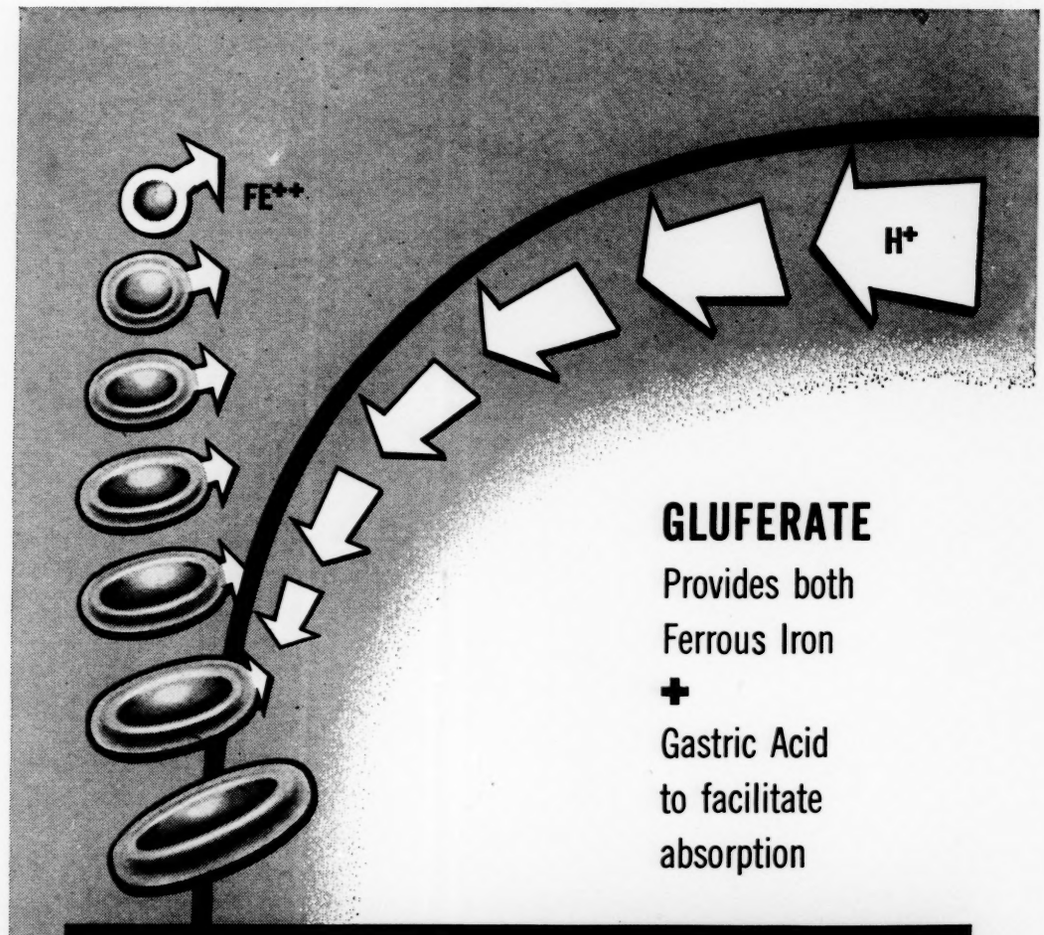

*Among the richest known sources of vitamin C are the citrus fruits. They also contain vitamins A, $B_1$ and P, and readily assimilable natural fruit sugars, together with other factors such as iron, calcium, citrates and citric acid.

*References:*

1. Gordon, E. S.: Nutritional and Vitamin Therapy in General Practice, Year Book Pub., 3rd ed., 1947.
2. Manchester, T. C.: Food Research, 7:394, 1944.
3. McLester, J. S.: Nutrition and Diet, Saunders, 4th ed., 1944.
4. Rose, M. S.: Rose's Foundation of Nutrition, rev. by Taylor and Macleod, Macmillan, 4th ed., 1944.
5. Sherman, H. C.: Chemistry of Food and Nutrition, Macmillan, 7th ed., 1946.

# FLORIDA

***Oranges • Grapefruit • Tangerines***




**GLUFERATE**
Provides both
Ferrous Iron
✚
Gastric Acid
to facilitate
absorption

**Of the three factors** that favor absorption of iron:[1]
(1) Iron in the ferrous state;
(2) Acid reaction in the stomach;
(3) Increased need for iron.

**GLUFERATE®**

Ferrous Sulfate and Glutamic Acid Hydrochloride Wyeth
**provides** *both* of the external factors

*Ferrous Sulfate*—A most efficiently absorbed form of iron.
*Glutamic Acid Hydrochloride*—Potent in correction of hypoacidity; assures prompt benefit with minimal distress.

SUPPLIED: Bottles of 100 tablets

1. Barer, A. P., and Fowler, W. M.: J. Lab. & Clin. Med. 34:932, 1949.

for
"double
insurance"
in
iron-deficiency
anemias

Wyeth Incorporated • Philadelphia 3, Pa.

Wyeth


# VERILOID*

*Product of Riker Research*

*A potent alkaloidal fraction of Veratrum viride—biologically standardized for hypotensive activity in mammals—a new active principle not heretofore available, for the treatment of hypertension.*

**BIOLOGICALLY STANDARDIZED IN MAMMALS.** Veriloid is carefully standardized in dogs; drop in blood pressure is used as the end point. In consequence, its hypotensive activity does not vary from tablet to tablet, from bottle to bottle, or from batch to batch. It is the first preparation of its kind available for clinical use.

**PROMPT CLINICAL RESPONSE.** The effect of Veriloid on the blood pressure is apparent within an hour or two after administration. While individualization of dosage is essential for maximum benefit, in the majority of patients the average dose of 2.0 mg. to 5.0 mg. three or four times daily after meals and at bedtime leads to a significant, sustained drop in arterial tension with concomitant subjective improvement.

**PROLONGED THERAPY POSSIBLE.** In most patients, treatment with Veriloid may be continued as long as necessary. Unlike many other hypotensive agents, Veriloid usually may be given without decrease in therapeutic effect, since drug tolerance is not likely to develop. Frequently, reduction in dosage is possible as the circulatory system improves from the lowered arterial tension.

*Veriloid is available on prescription through all pharmacies in slow dissolving tablets containing 1.0 mg., in bottles of 100 and 200.*

*Trade Mark Riker Laboratories, Inc.

**RIKER LABORATORIES, INC., 8480 BEVERLY BLVD., LOS ANGELES**


# Potency---
# 15 mcg.
# Vitamin B 12
# per fl. oz.

+

- High potency ferrous iron—Fe 3 gr.
- Soluble constituents from 2 ounces whole fresh beef liver
- Vitamin B complex factors in substantial amounts

## BĒPRON®
## FORTIFIED

**BEEF LIVER WITH IRON, FOLIC ACID, THIAMINE, RIBOFLAVIN AND NIACINAMIDE**

**Palatable and well tolerated: assures rapid and sustained benefit.**

Wyeth®

*Wyeth*

**Incorporated**
**Philadelphia 3, Pa.**

# *A Real American Breakfast*

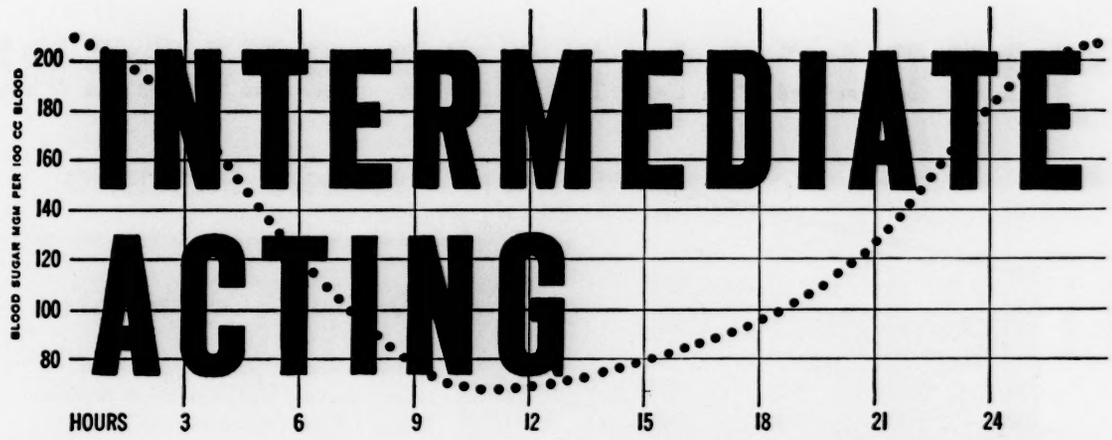
That a nutritious breakfast providing generous amounts of high quality protein prevents late morning hypoglycemia has been amply demonstrated. As shown by Thorn and co-workers,[1] and later confirmed by Orent-Keiles,[2] ". . . breakfast high in protein and low in fat and carbohydrate was followed by an improved sense of well-being and no symptoms of hypoglycemia."

Breakfast meats—ham, sausage, bacon, breakfast steaks—are an appetizing means of increasing the protein content of the morning meal. Their biologically complete protein contains all essential amino acids, and serves well in complementing less complete proteins from other sources. Furthermore, muscle meat is an outstanding source of B complex vitamins and of iron.

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

(1) Thorn, G.W.; Quinby, J.T., and Marshall, C., Jr., Ann. Int. Med. 18:913 (June) 1943.
(2) Orent-Keiles, E., and Hallman, L.F., Circular No. 827, United States Department of Agriculture, Bureau of Human Nutrition and Home Economics, Agricultural Research Administration, Dec., 1949.

**American Meat Institute**
**Main Office, Chicago... Members Throughout the United States**




# INTERMEDIATE ACTING

# GLOBIN INSULIN

## 'B.W.& CO.'

*...was developed to fill the "need for an insulin with activity intermediate between that of regular insulin and that of protamine zinc insulin."*[1]

**IN 1939,** Reiner, Searle and Lang described a new "intermediate acting" insulin.

**IN 1943,** after successful clinical testing, the new substance was released to the profession as 'Wellcome' brand Globin Insulin with Zinc 'B. W. & Co.'

**TODAY,** according to Rohr and Colwell, "Fully 80% of all severe diabetics can be balanced satisfactorily"[2] with Globin Insulin 'B.W. & Co.'—or with a 2:1 mixture of regular insulin: protamine zinc insulin. *Ready-to-use* Globin Insulin 'B. W. & Co.' provides the desired intermediate action without preliminary mixing in vial or syringe.

*In 10 cc. vials, U-40 and U-80.*

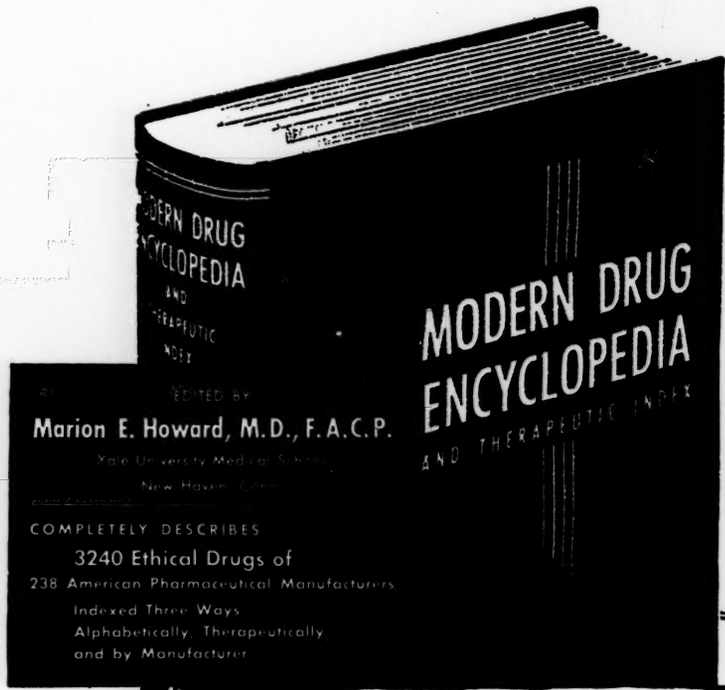

'B.W.& CO. —*a mark to remember*

1. Rohr, J.H., and Colwell, A.R.: Arch. Int. Med. 82:54, 1948.
2. Ibid Proc. Am. Diabetes Assn. 8:37, 1948.

**BURROUGHS WELLCOME & CO. (U.S.A.) INC.** Tuckahoe 7, New York

# A MEDICAL BEST SELLER!

**SECOND PRINTING**




1949 Edition
Bound in Red Fabricoid
1,200 pages, Size 2" x 6" x 9"
Price Postpaid $12 U.S.A.—
$14 Foreign

## Doctors' Comments

**"Please accept my congratulations on your excellent publication on Modern Drugs." K.S.G., M.D., Durham, N. C.**

**"I am finding it very useful." L.I.Y., M.D., Winona, Minn.**

**"Put my name down to send me a new one every time it comes off the press." D.H.A., M.D., Memphis, Tenn.**

**"I think this is one of the best publications in print." W.S., M.D., Augusta, Ga.**

*Typical Description*

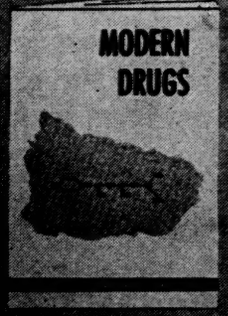
**$B_{12}$ CONCENTRATE** ***Hematopoietic*** **(Armour)**

DESCRIPTION: An aqueous solution containing 10 micrograms of vitamin $B_{12}$ per cc.

ACTION AND USES: Effects an adequate hematopoietic response in pernicious anemia cases; offers a substitute for liver therapy in the treatment of pernicious anemia patients who exhibit a sensitivity to liver extract. An important adjunct to liver therapy in the treatment of pernicious anemia, nutritional macrocytic anemia, non-tropical sprue and tropical sprue.

ADMINISTRATION: *Intramuscularly*, preferably in the gluteal muscle. In macrocytic anemia of pregnancy, 10 to 20 micrograms once a week until termination of pregnancy. In macrocytic anemia of infancy, 10 to 20 micrograms until blood count returns to normal. In nutritional anemia dosage may vary from 6 to 100 micrograms over a 14 day period to obtain an optimal response. In most pernicious anemia cases 25 micrograms per week results in an optimal response.

SUPPLY: $B_{12}$ CONCENTRATE—Vials, rubber-capped, 10 cc.




Kept up-to-date with four Modern Drug Supplements yearly

Drug Publications, Inc.
49 West 45th St., New York 19, N. Y.

Enclosed is the sum of twelve dollars ($12 U.S.A.) for which please send me postpaid the new Fourth Edition of the MODERN DRUG ENCYCLOPEDIA AND THERAPEUTIC INDEX AND MODERN DRUGS.

Name.....

Address.....

City..... Zone..... State.....

U.S.A. $12 Foreign $14

*One of a series of reports on*

# Cortone

TRADE-MARK

## Key to a New Era in Medical Science

First synthesized from a bile acid in the Merck Research Laboratories in 1946, Cortone* was used initially at the Mayo Clinic with dramatic results in the treatment of rheumatoid arthritis.

Since that time, clinical studies conducted by more than a thousand investigators have indicated a broad spectrum of usefulness for this hormonal substance.

As a result of steadily increasing production, adequate supplies of Cortone now are available for therapeutic use by the physician.

*Among the conditions in which Cortone has produced striking clinical improvement are:*

**RHEUMATOID ARTHRITIS** and Related Rheumatic Diseases

**ACUTE RHEUMATIC FEVER**

**BRONCHIAL ASTHMA**

**EYE DISEASES,** Including Nonspecific Iritis, Iridocyclitis, Uveitis, and Sympathetic Ophthalmia

**SKIN DISORDERS,** Notably Pemphigus, Angioneurotic Edema, Atopic Dermatitis, and Exfoliative Dermatitis, Including Cases Secondary to Drug Reactions

CORTONE Acetate (Cortisone Acetate Merck) is available to all hospitals registered by the American Medical Association. For the present, this drug is to be used, during the initial period of treatment, only in hospitalized patients.

# Cortone

TRADE-MARK

ACETATE

**(CORTISONE** Acetate Merck**)**

(11-Dehydro-17-hydroxycorticosterone-21-Acetate)

MERCK

**MERCK & CO., INC.**

*Manufacturing Chemists*

RAHWAY, NEW JERSEY

**Trade-mark of Merck & Co., Inc. for its brand of cortisone.*

# How effective is ACNOMEL in ACNE?

## New evidence from a comprehensive study*

100 patients with acne were treated with Acnomel—S.K.F.'s rapid-acting, lesion-masking acne preparation. Writing in *The Journal of the A.M.A.*, the author reports of Acnomel—

"Acne was either arrested or decidedly improved in all cases."

Flesh-tinted Acnomel "matched the average skin, enabled the patient to cover the lesions and thus prevented embarrassment" and psychological trauma.

In Acnomel you have, for the first time, a preparation which meets the essential therapeutic and cosmetic requirements for the successful topical treatment of acne. Acnomel contains resorcinol, 2%, and sulfur, 8%, in a special grease-free vehicle.

*Dexter, H.: Studies in Acne, J.A.M.A. 142:715 (March 11) 1950

# ACNOMEL

a significant advance,

clinical and cosmetic,

in acne therapy

Smith, Kline & French Laboratories, Philadelphia

'Acnomel' T.M. Reg. U.S. Pat. Off.